Audet 10_602035- - History

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=> d his ful

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L7             STR
L8            6 SEA SUB=L6 SSS FUL L7

     FILE 'HCAPLUS' ENTERED AT 10:22:49 ON 28 JUL 2006
L9           16 SEA ABB=ON  PLU=ON  L8
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L10      176900 SEA ABB=ON  PLU=ON  VPF/SQSP
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L12         267 SEA ABB=ON  PLU=ON  L6 NOT L8

     FILE 'HCAPLUS' ENTERED AT 10:29:42 ON 28 JUL 2006
L13         214 SEA ABB=ON  PLU=ON  L12
L14       91667 SEA ABB=ON  PLU=ON  L11 OR ?PHOSPHONAT?
L15           1 SEA ABB=ON  PLU=ON  L13 AND L14
L16           1 SEA ABB=ON  PLU=ON  L15 NOT L9
               D STAT QUE L16
               D IBIB ABS HITSTR L16 1
L17       22549 SEA ABB=ON  PLU=ON  L10
L22       18010 SEA ABB=ON  PLU=ON  ?ADHES?(L)TISSUE
L23           0 SEA ABB=ON  PLU=ON  L22 AND L18
L24        1075 SEA ABB=ON  PLU=ON  VPF OR VAL?(2W)PRO?(2W)PHE?
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L34         453 SEA ABB=ON  PLU=ON  MIYAZAKI M/AU OR MIYAZAKI MIZUO/AU
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               D STAT QUE L35
               D IBIB ABS HITSTR L35
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               L35)
               D STAT QUE L36
               D IBIB ABS HITSTR L36 1-4


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   26 JUL 2006  HIGHEST RN 896142-63-5
     DICTIONARY FILE UPDATES:  26 JUL 2006  HIGHEST RN 896142-63-5

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.
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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE HCAPLUS

FILE COVERS 1907 - 28 Jul 2006 VOL 145 ISS 6
FILE LAST UPDATED: 27 Jul 2006 (20060727/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:22:49 ON 28 JUL 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 28 Jul 2006  VOL 145 ISS 6
FILE LAST UPDATED: 27 Jul 2006  (20060727/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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=> d stat que l9
L4                STR
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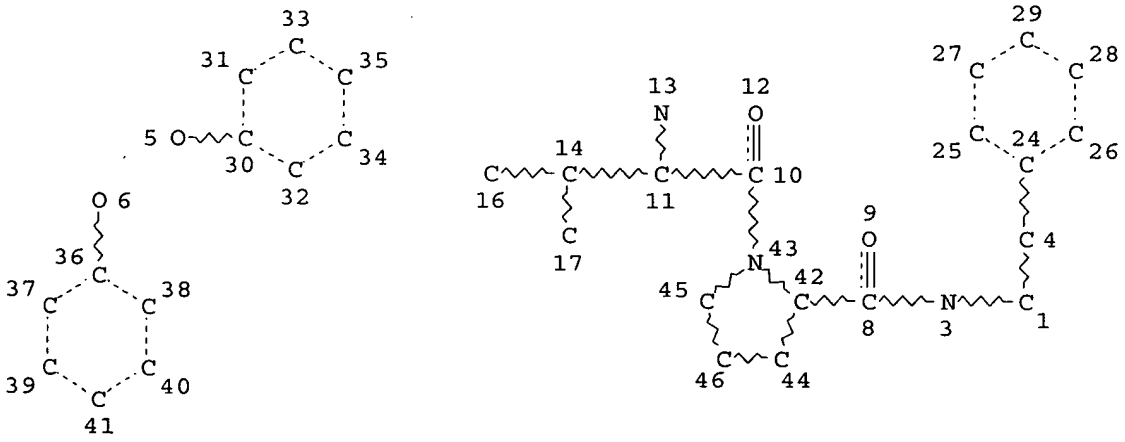

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  37

STEREO ATTRIBUTES: NONE
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L7               STR
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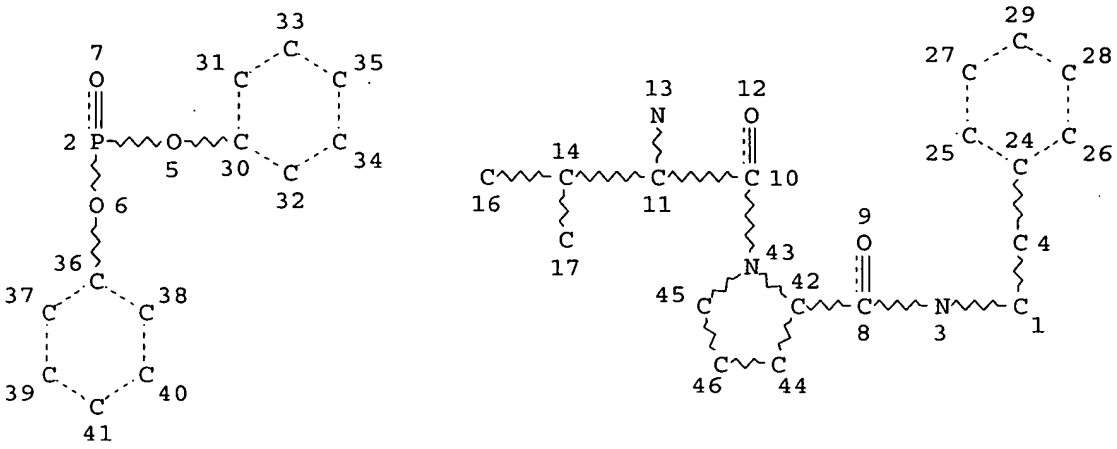

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 39

STEREO ATTRIBUTES: NONE
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L9 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L8

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L9 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1209247 HCAPLUS
DOCUMENT NUMBER: 144:32161
TITLE: Effect of chymase on intraocular pressure in rabbits
AUTHOR(S): Konno, Takashi; Maruichi, Midori; Takai, Shinji; Oku, Hidehiro; Sugiyama, Tetsuya; Uchibori, Takehiro; Nagai, Akihiko; Kogi, Kentaro; Ikeda, Tsunehiko; Miyazaki, Mizuo
CORPORATE SOURCE: Drug Research Section II, Fukushima Research Laboratories, TOA EIYO LTD., Fukushima City, Fukushima, 960-0280, Japan
SOURCE: European Journal of Pharmacology (2005), 524(1-3), 132-137
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chymase is a chymotrypsin-like serine protease that is stored exclusively in the secretory granules of mast cells and converts big endothelins to endothelin-1 (1-31). The aim of this study was to evaluate the effect of chymase on intraocular pressure in rabbits. Chymase injection (3 and 10 mU) resulted in a trend toward increased intraocular pressure and a significant increase in intraocular pressure at a dose of 10 mU compared

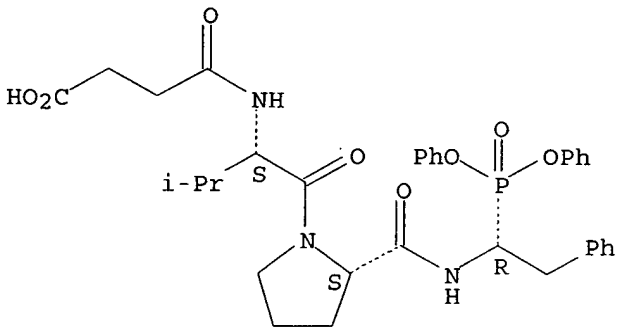
with the control. A specific chymase inhibitor, Suc-Val-Pro-PheP(OPh)2, attenuated the ocular hypertension induced by chymase. Endothelin-1 (1-31) also caused ocular hypertension, which was inhibited by a selective endothelin ETA receptor antagonist, cyclo(D-Asp-Pro-D-Val-Leu-D-Trp) (BQ-123). Moreover, chymase-induced ocular hypertension was inhibited by BQ-123. These results suggest that chymase influences the regulation of intraocular pressure, and it is likely that the formation of endothelin-1 (1-31) and subsequent activation of endothelin ETA receptors are involved in the development of ocular hypertension induced by chymase.

IT 174391-82-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of chymase on intraocular pressure in rabbits)

RN 174391-82-3 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1019891 HCAPLUS
DOCUMENT NUMBER: 141:420442
TITLE: Cardioprotective agent
INVENTOR(S): Miyazaki, Mizuo; Takai, Shinji
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004100988	A1	20041125	WO 2004-JP6384	20040512

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1640020 A1 20060329 EP 2004-732417 20040512

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

PRIORITY APPLN. INFO.: JP 2003-134487 A 20030513

WO 2004-JP6384 W 20040512

AB A medical agent capable of effective cardioprotection when the symptoms of hypertension, cardiomegaly, myocardial infarction, arteriosclerosis, diabetic or non-diabetic kidney diseases, arrhythmia accompanying re-stenosis, etc. after PTCA operation, cardiofibrosis and cardiac failure are concerned about. In particular, a medical agent comprising an effective amount of at least one protease inhibitor, i.v. or orally administered. The protease inhibitor is preferably a serine protease inhibitor which is specifically a chymotrypsin-like serine protease inhibitor. For example, use is made of a chymase inhibitor, viz. a peptide derivative of aryl diester of α-aminoalkylphosphonic acid represented by Suc-Val-Pro-PheP(OPh)2, preferably its enantiomer Suc-Val-Pro-L-PheP(OPh)2.

IT 130727-22-9P 174391-82-3P

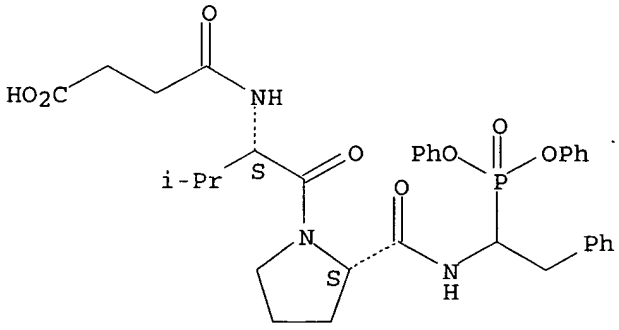
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(peptide derivs. of aryl diester of α-aminoalkylphosphonic acids as protease inhibitors and cardioprotective agents)

RN 130727-22-9 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

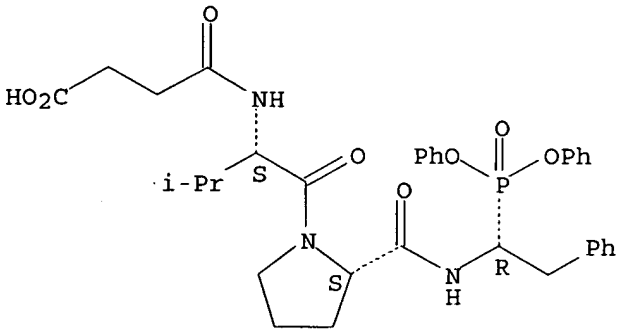
Absolute stereochemistry.



RN 174391-82-3 HCAPLUS

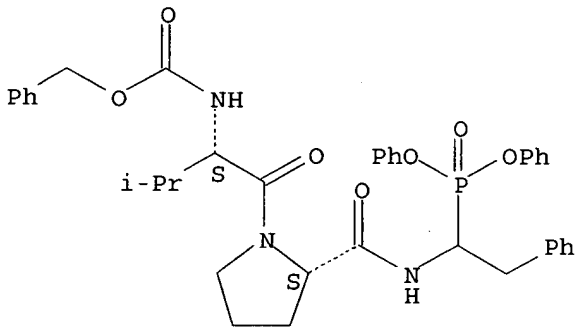
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 796865-77-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(peptide derivs. of aryl diester of α-aminoalkylphosphonic acids as protease inhibitors and cardioprotective agents)
RN 796865-77-5 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:675660 HCAPLUS
DOCUMENT NUMBER: 141:185127
TITLE: Drug for preventing, regulating or treating adhesion
INVENTOR(S): Miyazaki, Mizuo; Takai, Shinji
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004069276	A1	20040819	WO 2004-JP1111	20040204

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG

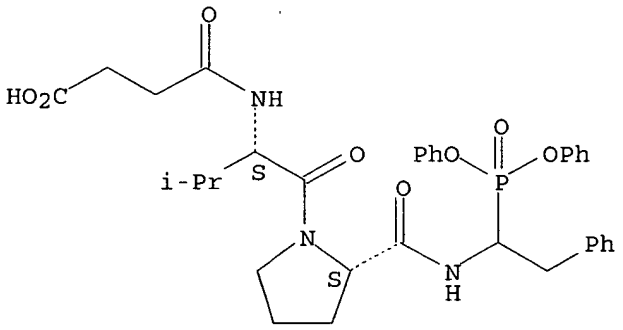
US 2006122101 A1 20060608 US 2005-544254 20050823
PRIORITY APPLN. INFO.: JP 2003-28743 A 20030205
WO 2004-JP1111 W 20040204

AB It is intended to provide a drug by which adhesion can be effectively prevented, regulated or treated in cases with the risk of visceral fusion caused by injury, inflammation, etc. before or after various surgical steps such as orthopedic or plastic surgeries relating to heart, breast, gynecol. cases, ophthalmic diseases and abdomen. Namely, a drug which contains at least one protease inhibitor in an ED and is to be used by i.v. administration, oral administration or transdermal application. It is preferable that the protease inhibitor is a serine protease inhibitor and the serine protease inhibitor is preferably a chymotrypsin-like serine protease inhibitor. As a specific example thereof, an α-aminoalkylsulfonic acid aryl diester peptide derivative Suc-Val-Pro-PheP(OPh)2, which is a chymase inhibitor, may be cited and an enantiomer Suc-Val-Pro-L-PheP(OPh)2, is preferred.

IT 130727-22-9 174391-80-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-aminoalkylsulfonic acid aryl diester peptide derivs. as protease and chymase inhibitors for preventing and treating adhesion after surgery)

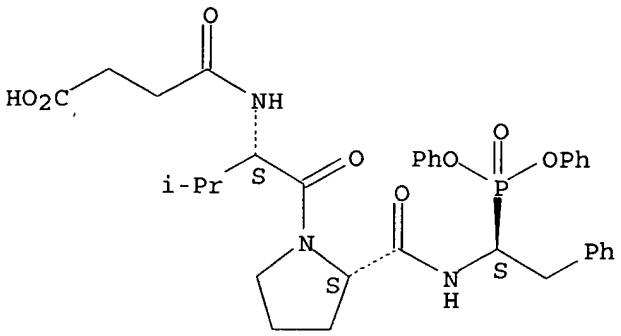
RN 130727-22-9 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 174391-80-1 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1S)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:351637 HCAPLUS
DOCUMENT NUMBER: 140:350627
TITLE: Chymase inhibitor-containing pharmaceuticals for surgery for glaucoma
INVENTOR(S): Miyazaki, Mizuo; Takai, Shinji
PATENT ASSIGNEE(S): Toa Eiyo, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

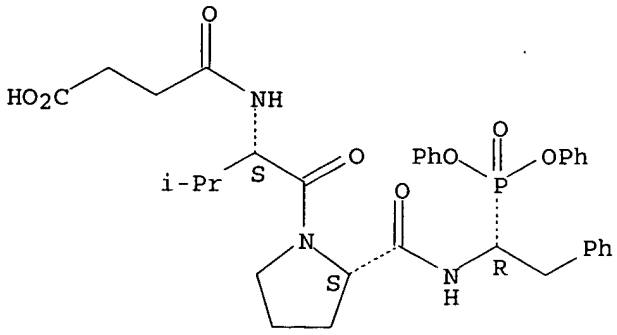
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004131442	A2	20040430	JP 2002-298825	20021011
PRIORITY APPLN. INFO.:			JP 2002-298825	20021011

AB Title pharmaceuticals contain (optically active) di-Ph 1-(N-succinyl-L-valyl-L-prolylamino)-2-phenylethanephosphonate (VPF) as active ingredient. Thus, application of VPF on sclera flap in trabeculectomy in dogs resulted in bleb formation rich in blood vessels with no tissue adhesion.

IT 174391-82-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of valylproline derivative as chymase inhibitor for surgery for glaucoma)

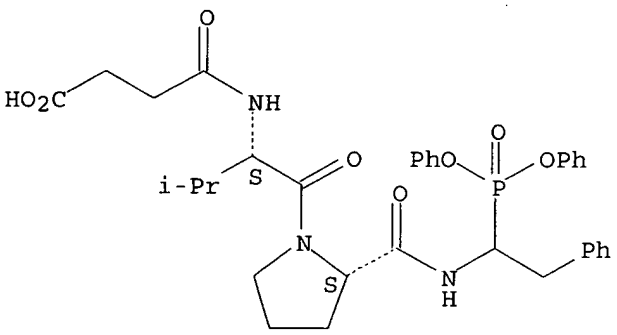
RN 174391-82-3 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



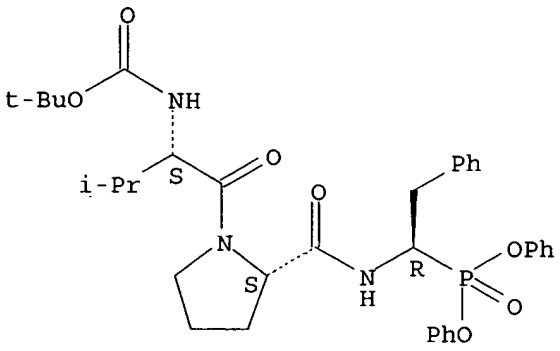
IT 130727-22-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of valylproline derivative as chymase inhibitor for surgery for glaucoma)
RN 130727-22-9 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 682335-85-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of valylproline derivative as chymase inhibitor for surgery for glaucoma)
RN 682335-85-9 HCAPLUS
CN L-Prolinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:184001 HCAPLUS
DOCUMENT NUMBER: 141:218544
TITLE: Attenuation of adhesion formation after cardiac surgery with a chymase inhibitor in a hamster model
AUTHOR(S): Soga, Yoshiharu; Takai, Shinji; Koyama, Tadaaki; Okamoto, Yukiko; Ikeda, Tadashi; Nishimura, Kazunobu; Miyazaki, Mizuo; Komeda, Masashi
CORPORATE SOURCE: Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, Kyoto, 606-8507, Japan
SOURCE: Journal of Thoracic and Cardiovascular Surgery (2004), 127(1), 72-78
CODEN: JTCSAQ; ISSN: 0022-5223
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: Chymase is one of the inflammatory mediators and is released from mast cells, which are closely associated with adhesion formation. Chymase also activates transforming growth factor β1, which promotes tissue fibrosis. However, the role of chymase in cardiac adhesion formation has not yet been elucidated. We have assessed whether a specific chymase inhibitor, Suc-Val-Pro-PheP (OPh)2, prevents postoperative cardiac adhesions in hamsters. Methods: In 66 hamsters the epicardium was abraded, and then either chymase inhibitor or placebo was injected into the left thoracic cavity, leaving the pericardium open. Cardiac chymase activity, the level of transforming growth factor β1 in the pleural fluid, and the d. of epicardial mast cells were measured 3 days postoperatively. The degree of adhesion formation was evaluated macroscopically and histol. 2 wk postoperatively by using a grading score ranging from 0 (no adhesions) to 4 (severe adhesions). Results: The cardiac chymase activity and level of transforming growth factor β1 were lower in the chymase inhibitor-treated group compared with in the placebo-treated group (45.8 ± 18.7 vs 79.7 ± 13.7 μU/mg protein [P < .025] and 15.6 ± 6.5 vs 33.2 ± 9.8 μg/mL [P < .01], resp.). The d. of mast cells was higher in the placebo-treated group, and there was suppression to 60% of this value in the chymase inhibitor-treated group. The adhesion scores were lower in the chymase inhibitor-treated group compared with in the placebo-treated group (1.3 ± 1.3 vs 3.0 ± 1.1, P < .01). Conclusion: Use of a chymase inhibitor suppresses not only cardiac chymase activity but also the level of transforming growth factor β1, and this results in a reduction in postoperative cardiac adhesion.

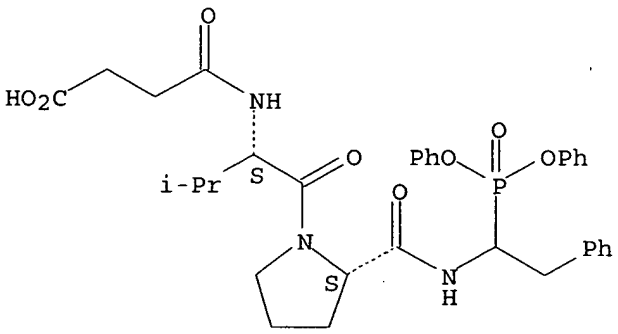
IT 130727-22-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(administration of specific chymase inhibitor Suc-Val-Pro-Phep (OPh)2 attenuates cardiac chymase activity, level of transforming growth factor β1 and postoperative cardiac adhesions in hamster model)

RN 130727-22-9 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:80335 HCAPLUS

DOCUMENT NUMBER: 140:122834

TITLE: Methods for preventing adhesion formation using peptidyl protease inhibitors

INVENTOR(S): Miyazaki, Mizuo

PATENT ASSIGNEE(S): Japan

SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004018984	A1	20040129	US 2003-602035		20030623
PRIORITY APPLN. INFO.:			US 2002-396493P	P	20020717

AB The present invention generally provides methods for the prevention or reduction of adhesion formation/reformation using protease inhibitors. More specifically, this invention provides methods for preventing or inhibiting postoperative adhesion formation/reformation in mammals following surgical or accidental injury or inflammation to the organs of the peritoneal or pleural cavity or other body spaces, using serine protease inhibitors, such as, for example, using chymase inhibitors (e.g., α-aminoalkylphosphonate derivs.) and the like.

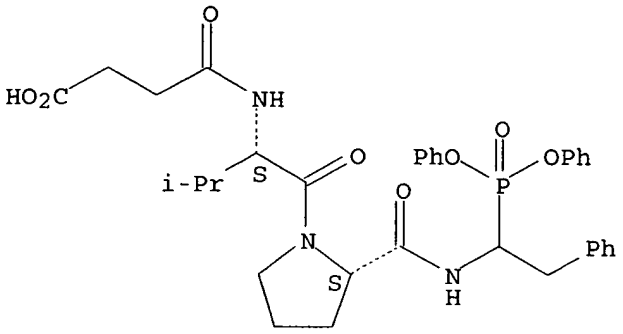
IT 130727-22-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptidyl protease inhibitors and use in preventing adhesion formation after surgery)

RN 130727-22-9 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-

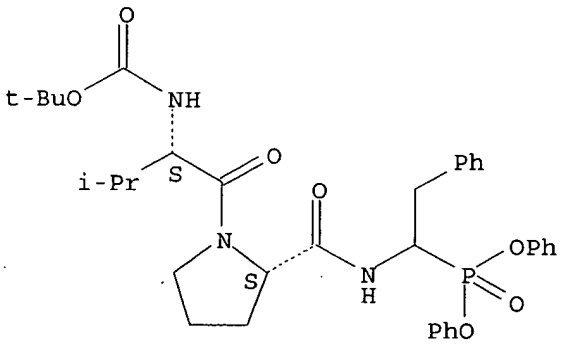
(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 651034-42-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptidyl protease inhibitors and use in preventing adhesion formation after surgery)
RN 651034-42-3 HCAPLUS
CN L-Prolinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:929299 HCAPLUS
DOCUMENT NUMBER: 139:110840
TITLE: Chymase inhibitors and their therapeutic potential
AUTHOR(S): Akahoshi, Fumihiko
CORPORATE SOURCE: Research Laboratory II, Pharmaceuticals Research Unit, Mitsubishi Pharma Corp., Kamoshida-cho, Aoba-ku, Yokohama, 227-0033, Japan
SOURCE: Drugs of the Future (2002), 27(8), 765-770
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Chymase is thought to play important roles in several biol. reactions. With the recent discovery of potent chymase inhibitors featuring specificity and metabolic stability, their potential clin.

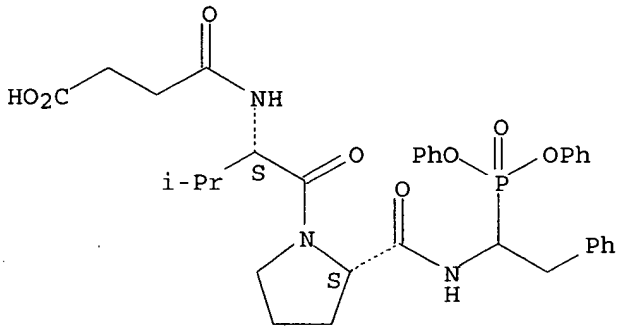
application has widened. Here, chymase inhibitors and their therapeutic potential in chymase-induced disease are addressed. Topics include peptidic chymase inhibitors, non-peptidic chymase inhibitors, and therapeutic potential of chymase inhibitors in restenosis after bypass graft or PTCA, tissue adhesion, angiogenesis-related diseases and atopic dermatitis.

IT 130727-22-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chymase inhibitors and their therapeutic potential)

RN 130727-22-9 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:761196 HCAPLUS

DOCUMENT NUMBER: 138:314202

TITLE: Lengthy suppression of vascular proliferation by a chymase inhibitor in dog grafted veins

AUTHOR(S): Tsunemi, Koutaro; Takai, Shinji; Nishimoto, Masayoshi; Yuda, Atsushi; Jin, Denan; Sakaguchi, Masato; Sawada, Yoshihide; Asada, Kunio; Kondo, Keiichiro; Sasaki, Shinjira; Miyazaki, Mizuo

CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, 569-8686, Japan

SOURCE: Journal of Thoracic and Cardiovascular Surgery (2002), 124(3), 621-625
CODEN: JTCSAQ; ISSN: 0022-5223

PUBLISHER: Mosby, Inc.

DOCUMENT TYPE: Journal

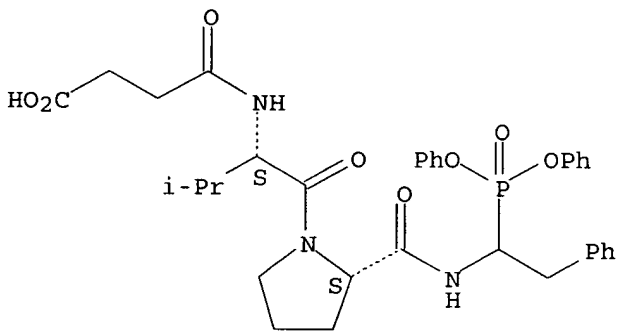
LANGUAGE: English

AB In this study the authors investigated the longterm effect of the chymase inhibitor Suc-Val-Pro-Phep(OPh)2 on intimal hyperplasia in dog grafted veins after bypass surgery. Twelve beagle dogs were studied. ACE and chymase activities, as well as total angiotensin II-forming activity were reported; and intimal area, medial area and ratio of intimal area to medial area were given. The results demonstrated that direct and single infiltration of grafting veins to a chymase inhibitor maintained suppression of chymase activity and vascular proliferation 3 mo after bypass surgery.

IT 130727-22-9

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lengthy suppression of vascular proliferation by chymase inhibitor in dog grafted veins in relation to prevention of intimal hyperplasia)
RN 130727-22-9 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

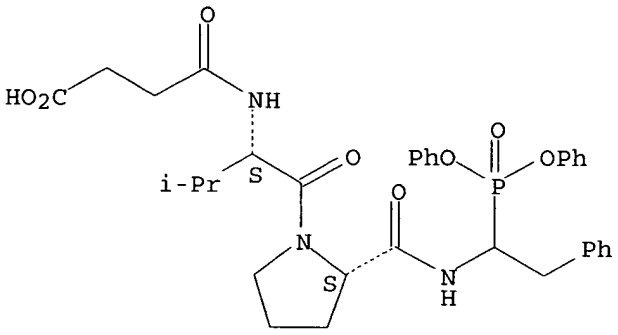


REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:371857 HCAPLUS
DOCUMENT NUMBER: 137:166726
TITLE: Effects of chymase on human dermal microvascular endothelial cells and human dermal fibroblasts
AUTHOR(S): Tanabe, Yuko; Soma, Yoshinao; Takai, Shinji; Miyazaki, Mizuo; Mizoguchi, Masako
CORPORATE SOURCE: Dep. Dermatol., St. Marianna Univ. Sch. Med., Kawasaki, 216-8511, Japan
SOURCE: Nippon Hifuka Gakkai Zasshi (2002), 112(3), 239-246
CODEN: NHKZAD; ISSN: 0021-499X
PUBLISHER: Nippon Hifuka Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Chymase is a proteolytic enzyme present in mast cell granules that is released by mast cell degranulation with tryptase, histamines, and other mediators. To elucidate the roles of mast cells in various biol. processes, including fibrosis and wound repair, it is necessary to know the effects of chymase on fibroblasts and vascular endothelial cells. We examined the effect of human chymase on human dermal microvascular endothelial cells (HDMEC) and human dermal fibroblasts (HDF). Chymase did not affect HDMEC growth, but it did stimulate the proliferation of HDF at 1 nM concentration This growth-promoting activity was completely inhibited by the addition of the chymase substrate peptide, Suc-Val-Pro-PheP(OPh)2. Chymase did not have any effect on ICAM-1 or VCAM-1 expression in HDMEC and HDF. The present study suggests that the mitogenic effect of chymase released from mast cells on dermal fibroblasts may be involved in some pathol. and physiol. processes. Another chymase inhibitory agent, which is a quinazoline derivative, stimulated the growth of HDMEC and enhanced VCAM-1 expression in the cells, suggesting an angiogenic effect.
IT 130727-22-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effects of chymase on human dermal microvascular endothelial cells and

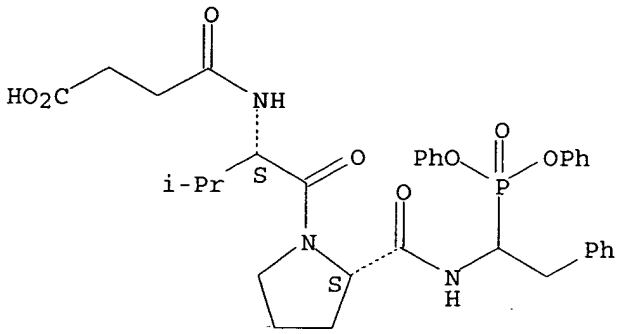
human dermal fibroblasts)
RN 130727-22-9 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:89522 HCAPLUS
DOCUMENT NUMBER: 137:393
TITLE: Chymase inhibitor suppresses adhesion formation in a hamster experimental model
AUTHOR(S): Okamoto, Yukiko; Takai, Shinji; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, 589-8686, Japan
SOURCE: European Journal of Pharmacology (2002), 435(2-3), 265-267
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To clarify the role of chymase produced by mast cells in adhesion formation, we investigated the preventive effect of a specific chymase inhibitor, Suc-Val-Pro-Phep (OPh)2, on adhesion formation in a hamster exptl. model. Hamsters underwent resection of the right uterine body and then 10 μM Suc-Val-Pro-Phep (OPh)2 or placebo was injected into the abdomen. Two weeks after the operation, the scores for adhesion formation in the chymase inhibitor-treated group were significantly lower than that in the placebo-treated group (placebo-treated group, 3.60±0.22; chymase inhibitor-treated group, 2.10±0.22; $P<0.01$). This specific chymase inhibitor, Suc-Val-Pro-Phep (OPh)2, significantly suppressed the scores for adhesion formation in a hamster exptl. model. Thus, chymase may play an important role in the adhesion formation.
IT 130727-22-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chymase inhibitor suppresses adhesion formation in a hamster exptl. model)
RN 130727-22-9 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

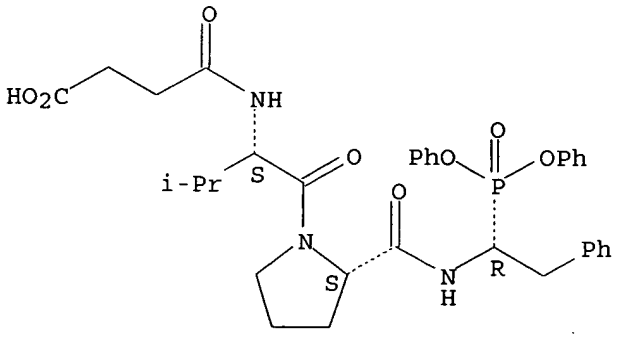
L9 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:435917 HCAPLUS
DOCUMENT NUMBER: 133:318923
TITLE: Aminophosphonic and aminophosphinic acid derivatives in the design of transition-state analogue inhibitors: biomedical opportunities and limitations
AUTHOR(S): Oleksyszyn, Jozef
CORPORATE SOURCE: Dyax Corporation, Cambridge, MA, USA
SOURCE: Aminophosphonic and Aminophosphinic Acids (2000), 537-557. Editor(s): Kukhar, Valery Pavlovich; Hudson, Harry R. John Wiley & Sons Ltd.: Chichester, UK. CODEN: 69ABMI
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB The design of transition-state (TS) analog inhibitors involves the replacement of key enzyme substrate moieties by structurally related mimetics. Aminophosphonic and aminophosphinic acid derivs. are classical examples of such compds., demonstrating that replacement of the carboxylic amino acid moiety provides excellent transition-state analog-type inhibitors for proteolytic enzymes. In addition, phosphonic and phosphinic acid residues can used in the design of hydrolytically stable phosphate mimics of peptides which contain O-phosphorylated tyrosine, serine and threonine. Although it is clear that the utility of aminophosphonic and aminophosphinic acids in drug design is much broader than the simple analogy to amino carboxylic acids would imply, this analogy nonetheless provides the most elegant examples of rational drug design described in the literature. The proteolytic enzymes are primary targets for compds. of this type, and several chapters in the present volume describe in detail the use of phosphonate-type inhibitors for specific enzymes such as HIV aspartyl protease, human collagenase, and thrombin. General principles for the design of TS analog types of inhibitors for proteolytic enzymes are provided in this chapter, along with discussion concerning the importance of some proteolytic enzymes as targets for drug development. Some new data is included which concerns the activity of aminophosphonic-type inhibitors in cell or tissue culture and in the animal model.

IT 174391-82-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(phenylalanine-related phosphonates Cbz-PheP(OPh)2 and Suc-Val-Pro-PheP(OPh)2 inhibit human heart chymase)
RN 174391-82-3 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

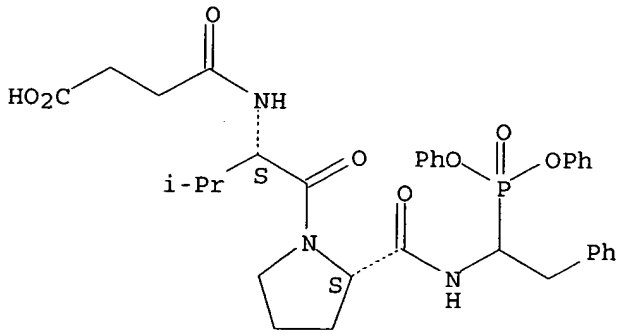
L9 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:95832 HCAPLUS
DOCUMENT NUMBER: 132:274101
TITLE: Inhibition of chymase reduces vascular proliferation in dog grafted veins
AUTHOR(S): Takai, S.; Yuda, A.; Jin, D.; Nishimoto, M.; Sakagichi, M.; Sasaki, S.; Miyazaki, M.
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, Japan
SOURCE: FEBS Letters (2000), 467(2,3), 141-144
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the effect of a chymase inhibitor Suc-Val-Pro-PheP(OPh)2 on the proliferation of the grafted vein in dog. By 28 days after the operation, the mean intimal area of the grafted vein in the placebo group was 3.24±0.32 mm2. The intimal area of the grafted vein in the chymase inhibitor-treated group was reduced to 63.9%. In the placebo group, the activities of chymase and angiotensin-converting enzyme in grafted vein were significantly increased 15- and 2-fold, resp. In the chymase inhibitor-treated group, chymase activity in the grafted veins was decreased significantly. These findings suggest that inhibition of chymase appears useful for preventing vascular proliferation.

IT 130727-22-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of chymase reduces vascular proliferation in dog grafted veins)

RN 130727-22-9 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

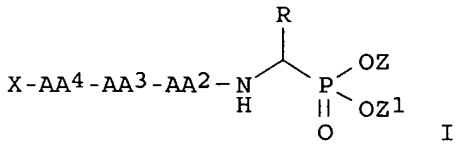


REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

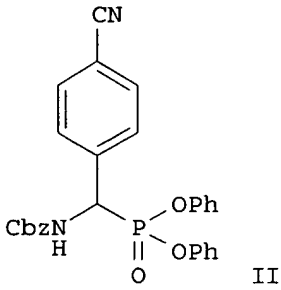
L9 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:735918 HCAPLUS
DOCUMENT NUMBER: 128:3887
TITLE: Preparation of basic α-aminoalkylphosphonate derivatives as serine protease inhibitors
INVENTOR(S): Powers, James C.; Boduszek, Bogdan; Oleksyszyn, Jozef
PATENT ASSIGNEE(S): Georgia Tech Research Corp., USA
SOURCE: U.S., 16 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5686419	A	19971111	US 1994-184286	19940121
US 5952307	A	19990914	US 1997-907840	19970814
PRIORITY APPLN. INFO.:			US 1994-184286 A2	19940121

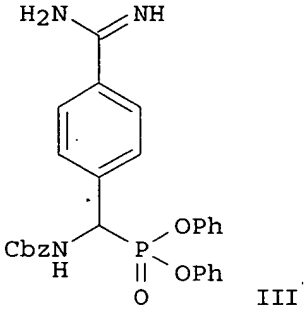
OTHER SOURCE(S): MARPAT 128:3887
GI



I



II



III

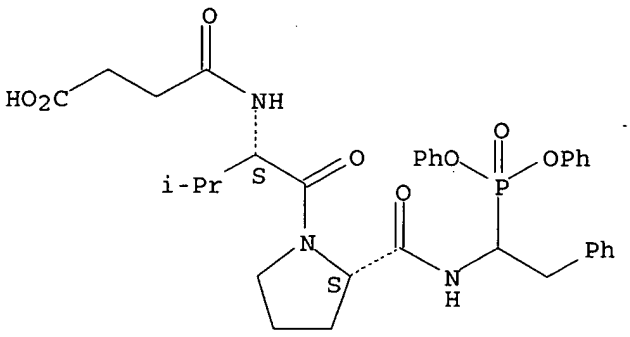
AB Peptidyl α-aminoalkylphosphonic acid diesters with basic substituents I [R = Ph, CH2Ph, C1-6 alkyl substituted with amidino, guanidino, isothioureido, or amino; Z, Z1 = independently C1-6 perfluoroalkyl, Ph, Ph substituted with 0-3 halo, C1-6 alkyl, C1-6 perfluoroalkyl, C1-6 alkoxy, NO2, CN, OH, CO2H, amino, C1-6 alkylamino, C2-12 dialkylamino, C1-6 acyl, C1-6 alkoxycarbonyl, C1-6 alkylthio; AA2, AA3, AA4 = independently bond, blocked or unblocked D-, L-, or achiral amino acid residue; X = H, NH2CO, NH2CS, NH2SO2, YNHCO, YNHCS, YNHSO2, YCS, YSO2, YO2C, YCO; Y = (un)substituted C1-6 alkyl, C1-6 fluoroalkyl, Ph, naphthyl, C1-6 alkylphenyl] and pharmaceutically acceptable salts thereof are prepared as compds. for use in inhibiting serine proteases with trypsin-like specificity and as anti-inflammatory agents, anticoagulants, and anti-tumor agents. Thus, condensation of 9.75 g 4-cyanobenzaldehyde with 7.65 g benzyl carbamate and 13.5 mL tri-Ph phosphite in 20 mL glacial acetic acid gave 70% cyanophenylphosphonate II. Amidination of II with ammonia and ammonium chloride in MeOH gave amidinophenyl derivative III as its HCl salt. III and related compds. were tested for inhibition of a variety of serine proteases.

IT 130727-22-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of basic α-aminoalkylphosphonate derivs. as serine protease inhibitors)

RN 130727-22-9 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

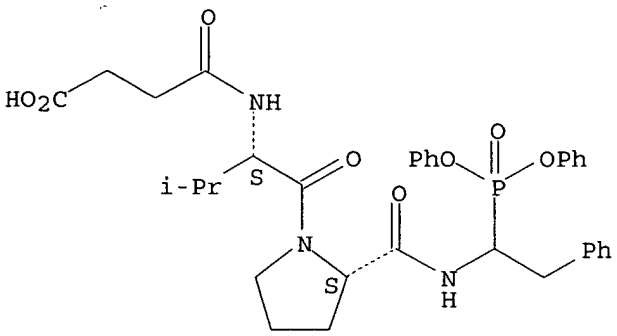


L9 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:687567 HCAPLUS
DOCUMENT NUMBER: 126:3707
TITLE: The 1.8 Å crystal structure of human cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)2: a Janus-faced proteinase with two opposite specificities
AUTHOR(S): Hof, Peter; Mayr, Irmgard; Huber, Robert; Korzus, Edward; Potempa, Jan; Travis, James; Powers, James C.; Bode, Wolfram
CORPORATE SOURCE: Max-Planck-Inst. Biochem., Planegg-Martinsried, D-82152, Germany
SOURCE: EMBO Journal (1996), 15(20), 5481-5491
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The crystal structure of human neutrophil cathepsin G, complexed with the peptidyl phosphonate inhibitor Suc-Val-Pro-PheP-(OPh)2, has been determined to a resolution of 1.8 Å using Patterson search techniques. The cathepsin G structure shows the polypeptide fold characteristic of trypsin-like serine proteinases and is especially similar to rat mast cell proteinase II. Unique to cathepsin G, however, is the presence of Glu226 (chymotrypsinogen numbering), which is situated at the bottom of the S1 specificity pocket, dividing it into two compartments. For this reason, the benzyl side chain of the inhibitor PheP residue does not fully occupy the pocket but is, instead, located at its entrance. Its pos. charged equatorial edge is involved in a favorable electrostatic interaction with the neg. charged carboxylate group of Glu226. Arrangement of this Glu226 carboxylate would also allow accommodation of a Lys side chain in this S1 pocket, in agreement with the recently observed cathepsin G preference for Lys and Phe at P1. The cathepsin G complex with the covalently bound phosphonate inhibitor mimics a tetrahedral substrate intermediate. A comparison of the Arg surface distributions of cathepsin G, leukocyte elastase and rat mast cell protease II shows no simple common recognition pattern for a mannose-6-phosphate receptor-independent targeting mechanism for sorting of these granular proteinases.

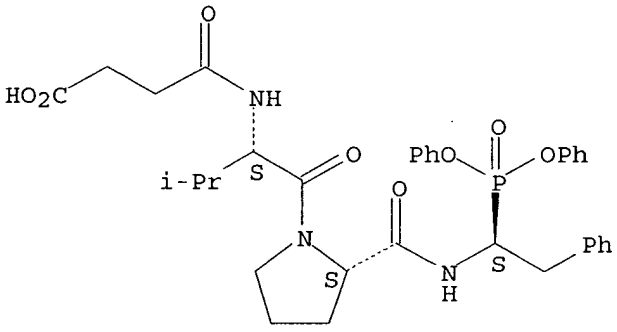
IT 130727-22-9D, complexes with cathepsin G
RL: PRP (Properties)
(crystal structure of human neutrophil cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)2)
RN 130727-22-9 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 174391-80-1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitor binding; crystal structure of human neutrophil cathepsin G in complex with Suc-Val-Pro-PheP-(OPh)2)
RN 174391-80-1 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1S)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

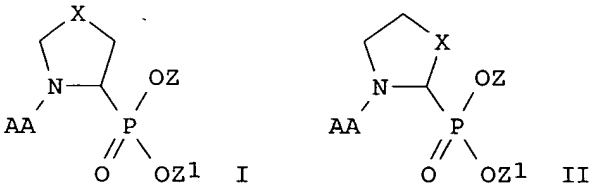
Absolute stereochemistry.



L9 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:153397 HCAPLUS
DOCUMENT NUMBER: 124:203102
TITLE: Preparation of peptide containing proline phosphonate derivatives as inhibitors of serine proteases
INVENTOR(S): Powers, James C.; Boduszek, Bogdan; Oleksyszyn, Jozef
PATENT ASSIGNEE(S): Georgia Tech. Research Corp., USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9529691	A1	19951109	WO 1995-US5345	19950428

W: CA, JP, MX
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
US 5543396 A 19960806 US 1994-234181 19940428
PRIORITY APPLN. INFO.: US 1994-234181 A 19940428
OTHER SOURCE(S): MARPAT 124:203102
GI



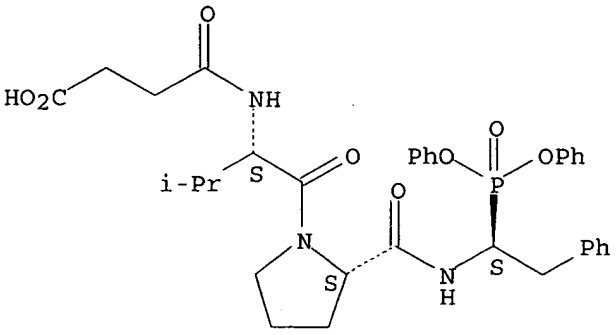
AB Peptidyl derivs. of diesters of α-aminoalkylphosphonic acids, particularly those with proline or related structures, [I and II; Z, Z1 = C1-6 perfluoroalkyl, (un)substituted Ph; X = a single bond, CH2, CH2CH2, (CH2)3, (CH2)4, Y, CH2Y, YCH2, (H,H); Y = O, S; AA = H, PhCH2O2C, H2NCHRCO (wherein R = C1-6 alkyl optionally fluorinated), β-alanine, glycine, ε-aminocaproic acid, sarcosine, side chain (un)blocked L-, D-, or DL-α-amino acid selected from the group consisting of alanine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, and etc.], useful for inhibiting serine proteases with chymotrypsin-like, trypsin-like, elastase-like, and dipeptidyl peptidase IV specificity and their roles as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents, are prepared Thus, to 0.36 g Boc-D-Phe-Pro-OH in 2 mL dry DMF at 0°, 0.17 g N,N'-dicyclohexylcarbodiimide was added. After stirring the mixture for 1 h, 0.45 g di-Ph amino(4-amidinophenyl)methanephosphonate dihydrochloride was added the solution was stirred for 48 h to give di-Ph N-(N-tert-butoxycarbonyl-D-phenylalanyl-L-prolyl)amino(4-amidinophenyl)methanephosphonate hydrochloride. H-Ala-ProP(OC6H4Cl-4)2.HCl and H-Ala-PipP(OC6H4Cl-4)2.HCl in vitro at 0.12 mM inhibited human placenta dipeptidylpeptidase IV (DPP-IV) at 0 and 88% after 2 min, resp., and 88 and 100%, resp., after 30 min.

IT 174391-80-1P 174391-82-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide containing proline phosphonate derivs. as inhibitors of
serine proteases for therapeutics)

RN 174391-80-1 HCAPLUS

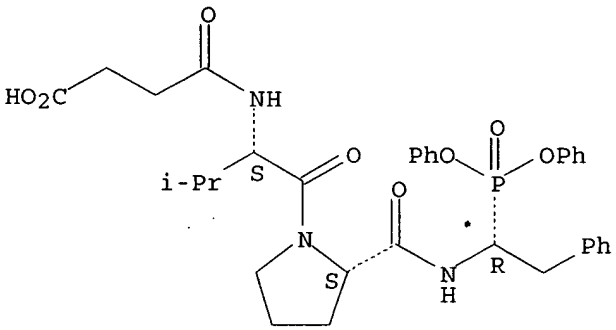
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1S)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 174391-82-3 HCAPLUS
CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[(1R)-1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:38271 HCAPLUS
DOCUMENT NUMBER: 114:38271
TITLE: Irreversible inhibition of serine proteases by peptide derivatives of (α-aminoalkyl)phosphonate diphenyl esters
AUTHOR(S): Oleksyszyn, Jozef; Powers, James C.
CORPORATE SOURCE: Sch. Chem., Georgia Inst. Technol., Atlanta, GA, 30332, USA
SOURCE: Biochemistry (1991), 30(2), 485-93
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 114:38271

AB Peptidyl derivs. of di-Ph (α-aminoalkyl)phosphonates have been synthesized and are effective and specific inhibitors of serine proteases at low concentration Z-PheP(OPh)2 (whereP(OPh)2 refers to the di-Ph phosphonate moiety) irreversibly reacts with chymotrypsin (kobsd/[I] = 1200 M-1 s-1) and does not react with 2 elastases. The best inhibitor for most chymotrypsin-like enzymes including bovine chymotrypsin, cathepsin G, and rat mast cell protease II is the tripeptide Suc-Val-Pro-PheP(OPh)2 which corresponds to the sequence of an excellent p-nitroanilide substrate for several chymases. The valine derivative Z-ValP(OPh)2 is specific for

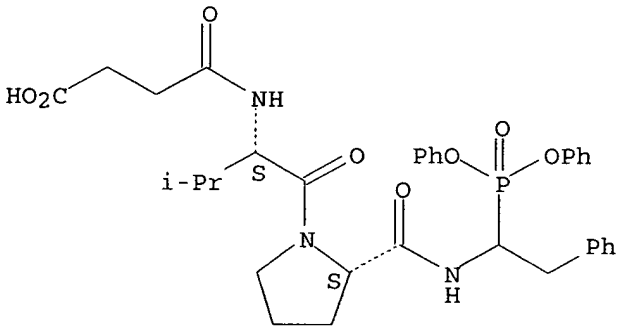
elastases and reacts with human leukocyte elastase (HLE, 280 M-1 s-1) but not with chymotrypsin. The tripeptide Boc-Val-Pro-ValP(OPh)2, which has a sequence found in a good trifluoromethyl ketone inhibitor of HLE, is the best inhibitor for HLE (kobsd/[I] = 27,000 M-1 s-1) and porcine pancreatic elastase (PPE, kobsd/[I] = 11,000 M-1 s-1). The rates of inactivation of chymotrypsin [by MeO-Suc-Ala-Ala-Pro-PheP(OPh)2] and PPE and HLE [by MeO-Suc-Ala-Ala-Pro-ValP(OPh)2] were decreased 2-5-fold in the presence of the corresponding substrate, which demonstrates active site involvement. Only one of two diastereomers of Suc-Val-Pro-PheP(OPh)2 reacts with chymotrypsin (146,000 M-1 s-1), and the enzyme-inhibitor complex had one broad signal at 25.98 ppm in the 31P NMR spectrum corresponding to the Ser-195 phosphonate ester. Phosphonylated serine proteases are extremely stable since the half-time for reactivation was >48 h for the inhibited elastases and 7.5-26 h for chymotrypsin. Peptidyl derivs. of di-Ph (α-aminoalkyl)phosphonates are relatively easy to synthesize, are chemical stable in buffer and in human plasma, form very stable derivs. with serine proteases, do not react with acetylcholinesterase, and thus should have considerable potential utility as therapeutic agents.

IT 130727-22-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and serine proteinases inactivation by, inhibitor structure and stereochem. in relation to)

RN 130727-22-9 HCAPLUS

CN L-Prolinamide, N-(3-carboxy-1-oxopropyl)-L-valyl-N-[1-(diphenoxyphosphinyl)-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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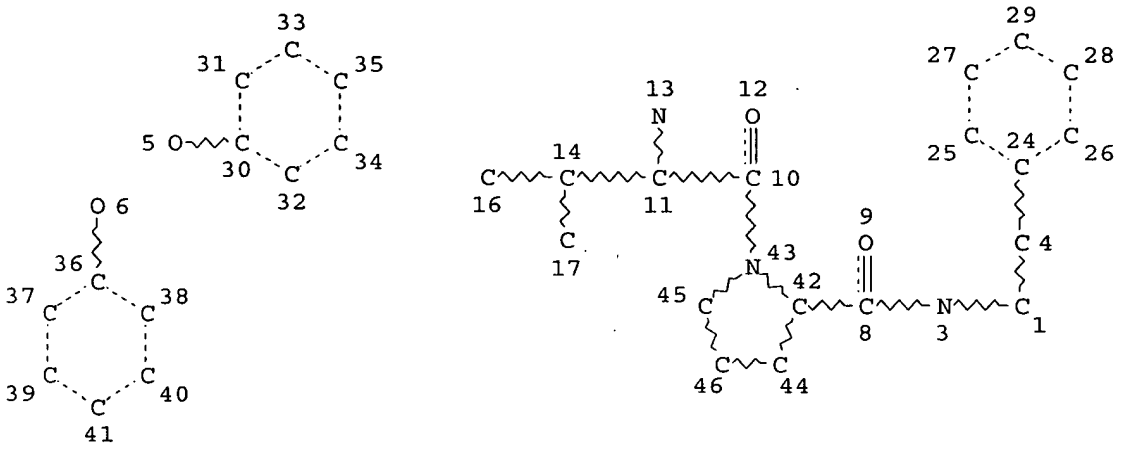

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 37

STEREO ATTRIBUTES: NONE
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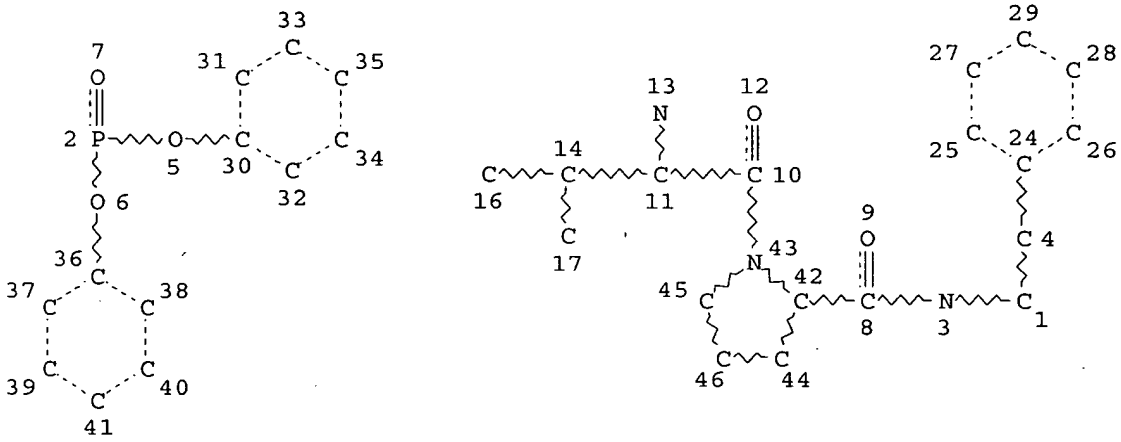
L7 STR



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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 39

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L9 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L8
L11 21544 SEA FILE=REGISTRY ABB=ON PLU=ON PHOSPHONATE/BI

```
L12          267 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L8
L13          214 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L14        91667 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 OR ?PHOSPHONAT?
L15            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 AND L14
L16            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 NOT L9


=>
=>

=> d ibib abs hitstr l16 1

L16  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1997:522873  HCAPLUS
DOCUMENT NUMBER:          127:172134
TITLE:                    The complete genome sequence of the gastric pathogen
                          Helicobacter pylori
AUTHOR(S):                Tomb, Jean-F.; White, Owen; Kerlavage, Anthony R.;
                          Clayton, Rebecca A.; Sutton, Granger G.; Fleischmann,
                          Robert D.; Ketchum, Karen A.; Klenk, Hans Peter; Gill,
                          Steven; Dougherty, Brian A.; Nelson, Karen;
                          Quackenbush, John; Zhou, Lixin; Kirkness, Ewen F.;
                          Peterson, Scott; Loftus, Brendan; Richardson, Delwood;
                          Dodson, Robert; Khalak, Hanif G.; Glodek, Anna;
                          McKenney, Keith; Fitzegerald, Lisa M.; Lee, Norman;
                          Adams, Mark D.; Hickey, Erin K.; Berg, Douglas E.;
                          Cocayne, Jeanine D.; Utterback, Teresa R.; Peterson,
                          Jeremy D.; Kelley, Jenny M.; Cotton, Matthew D.;
                          Weidman, Janice M.; Fujii, Claire; Bowman, Cheryl;
                          Watthey, Larry; Wallin, Erik; Hayes, William S.;
                          Borodovsky, Mark; Karp, Peter D.; Smith, Hamilton O.;
                          Fraser, Claire M.; et al.
CORPORATE SOURCE:         Inst. for Genomic Res., Rockville, MD, 20850, USA
SOURCE:                   Nature (London) (1997), 388(6642), 539-547
                          CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER:                Macmillan Magazines
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Helicobacter pylori, strain 26695, has a circular genome of 1,667,867 base
     pairs and 1590 predicted coding sequences.  Sequence anal. indicates that
     H. pylori has well-developed systems for motility, for scavenging iron,
     and for DNA restriction and modification.  Many putative adhesins,
     lipoproteins and other outer membrane proteins were identified,
     underscoring the potential complexity of host-pathogen interaction.  Based
     on the large number of sequence-related genes encoding outer membrane
     proteins and the presence of homopolymeric tracts and dinucleotide repeats
     in coding sequences, H. pylori, like several other mucosal pathogens,
     probably uses recombination and slipped-strand mispairing within repeats
     as mechanisms for antigenic variation and adaptive evolution.  Consistent
     with its restricted niche, H. pylori has a few regulatory networks, and a
     limited metabolic repertoire and biosynthetic capacity.  Its survival in
     acid conditions depends, in part, on its ability to establish a pos.
     inside-membrane potential in low pH.
IT   193839-09-7 193945-66-3
     RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
     (Biological study)
        (amino acid sequence; complete genome sequence of Helicobacter pylori)
RN   193839-09-7  HCAPLUS
CN   Alkylphosphonate transporter (Helicobacter pylori strain 26695 gene phnA)
     (9CI)  (CA INDEX NAME)
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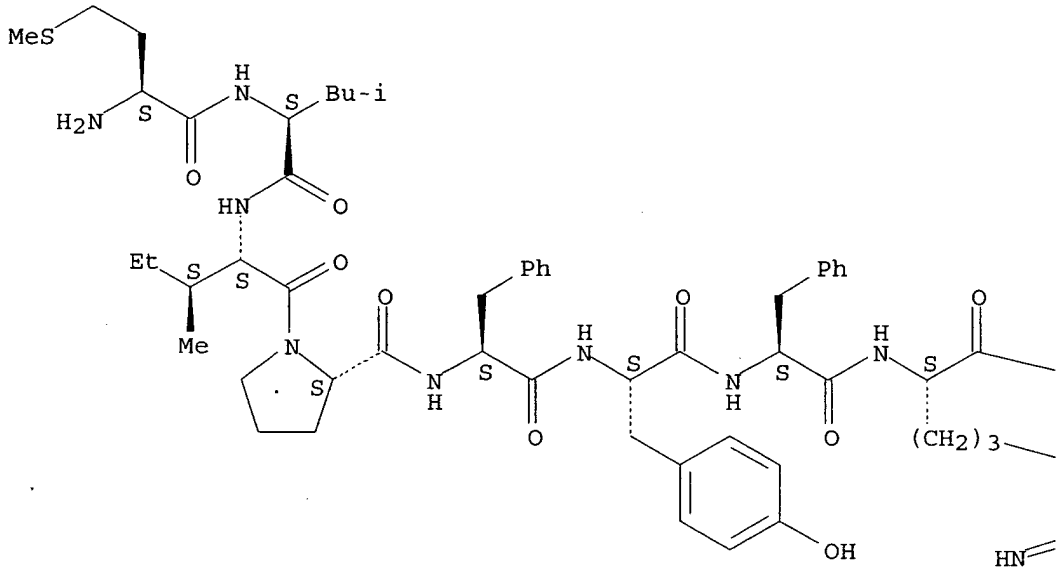
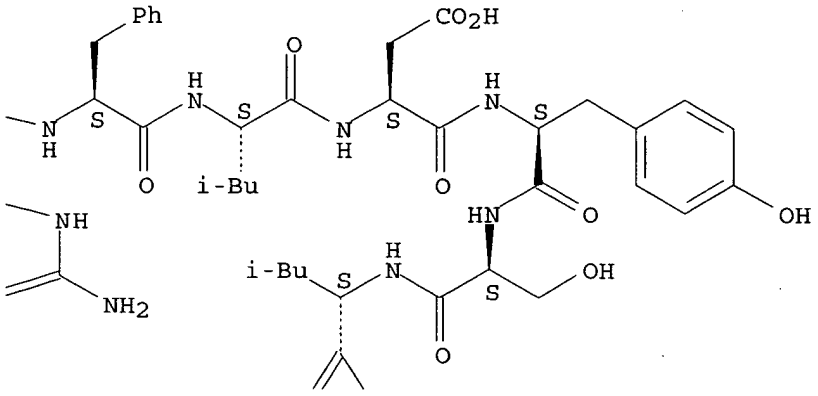
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 193945-66-3 HCAPLUS
CN L-Lysine, L-methionyl-L-leucyl-L-isoleucyl-L-prolyl-L-phenylalanyl-L-tyrosyl-L-phenylalanyl-L-arginyl-L-phenylalanyl-L-leucyl-L-α-aspartyl-L-tyrosyl-L-seryl-L-leucyl-L-lysyl-L-lysylglycyl-L-leucyl-L-valyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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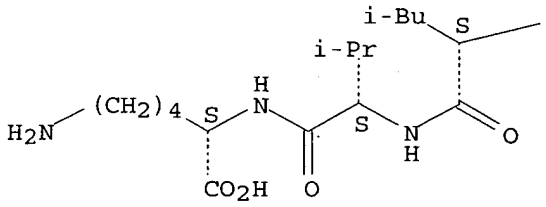
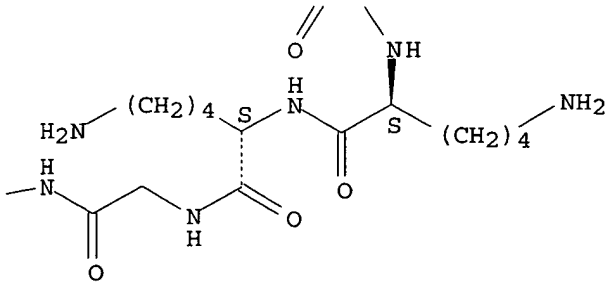


PAGE 2-B



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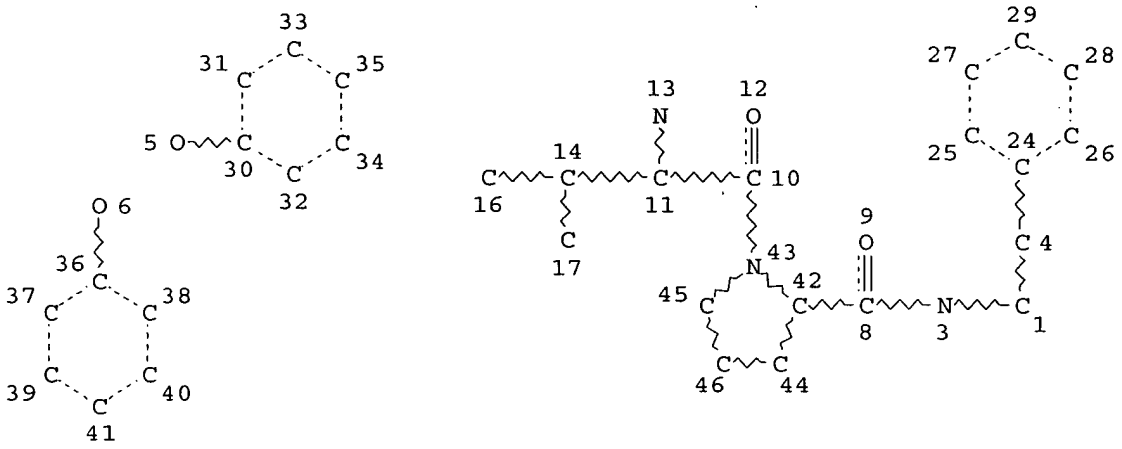

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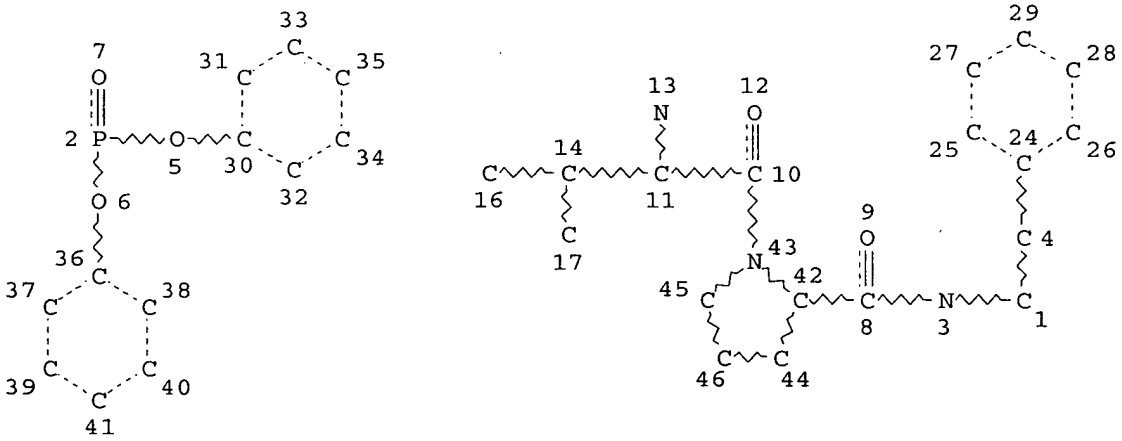
L7 STR



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NUMBER OF NODES IS 39

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L11       21544 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHOSPHONATE/BI
L12         267 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L8
L13         214 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L14       91667 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 OR ?PHOSPHONAT?
L15           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 AND L14
L16           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 NOT L9
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L26          26 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 AND L25
L27          14 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 NOT (L9 OR L16)


=> d ibib abs hitstr l27 1-14

L27  ANSWER 1 OF 14  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:902847  HCAPLUS
DOCUMENT NUMBER:          143:229574
TITLE:                    Preparation of acyloxy-amino-functionalized-aromatic
                          carboxy compounds as calcilytic compounds useful
                          against bone and mineral diseases
INVENTOR(S):              Marquis, Robert W., Jr.; Ramanjulu, Joshi M.;
                          Casillas, Linda N.
PATENT ASSIGNEE(S):       Smithkline Beecham Corporation, USA
SOURCE:                   PCT Int. Appl., 31 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2005077886         A1    20050825    WO 2005-US3500          20050204
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
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             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2004-542763P     P  20040206
OTHER SOURCE(S):          MARPAT 143:229574
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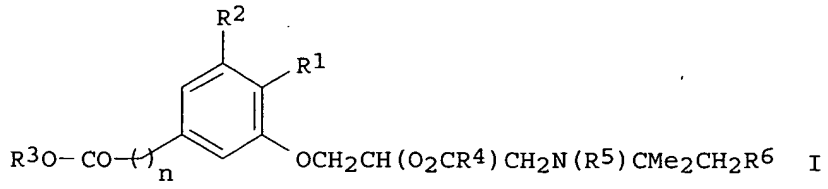

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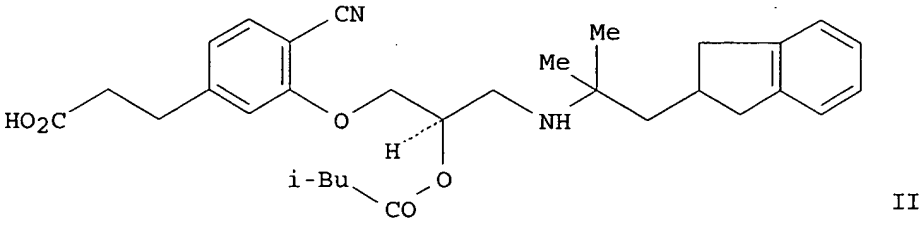


II

AB Novel calcilytic compds. (inhibitors of Ca receptor activity) (shown as I; R1 = H, CN, and halogen; R2 = halogen and H; R3 = H and (un)substituted C1-5 alkyl; n = 0-5; R4 = C1-7 alkyl and cycloalkyl; R5 is H or COR4; and R6 = aryl, fused aryl, dihydro, tetrahydro fused aryl, and heteroaryl, (un)substituted with OH, halogen, C1-4 alkyl, C1-4 alkoxy, CF,, OCF3, CN and NO2; e.g. 3-[4-cyano-3-[[(2R)-3-[[2-(2,3-dihydro-1H-inden-2-yl)-1,1-dimethylethyl]amino]-2-[(3-methylbutanoyl)oxy]propyl]oxy]phenyl]propanoic acid hydrochloride (free base shown as II)) and methods of using them are provided. No data is provided for the calcilytic activity of I. Although the methods of preparation are not claimed, 23 example prepns. are included. For example, II was prepared in 1 step (20 % yield) from 3-[4-cyano-3-[[(2R)-3-[[2-(2,3-dihydro-1H-inden-2-yl)-1,1-dimethylethyl]amino]-2-hydroxypropyl]oxy]phenyl]propanoic acid and isovaleric anhydride followed by HCl treatment.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:644733 HCAPLUS

DOCUMENT NUMBER: 143:242333

TITLE: Significance of chymase-dependent angiotensin II-forming pathway in the development of vascular proliferation

AUTHOR(S): Miyazaki, M.; Takai, S.

CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Japan

SOURCE: Heart Disease: Pathogenesis, Diagnosis and Treatment, Proceedings of the World Congress on Heart Disease: New Trends in Research, Diagnosis and Treatment, 3rd, Washington, DC, United States, July 12-15, 2003 (2004) , Meeting Date 2003, 77-82. Editor(s): Kimchi, Asher. Monduzzi Editore: Bologna, Italy.
CODEN: 69HBNK; ISBN: 88-7587-005-5

DOCUMENT TYPE: Conference; (computer optical disk)

LANGUAGE: English

AB Vascular tissues of human, monkey and dog contain chymase as an angiotensin II-forming enzyme. In this study, the authors investigated whether a chymase inhibitor prevents the development of vascular proliferation in dog grafted veins. The right external jugular vein of dog was grafted to the ipsilateral carotid artery. As a control group,

the right external jugular veins in non-operated dogs were used. In the chymase inhibitor-treated group, the vein was infiltrated with Suc-Val-Pro-Phep(OPh)2 and was grafted to the carotid artery. In the placebo-treated group, the angiotensin converting enzyme (ACE) activity in the grafted veins was significantly lower than that in the control veins up to 7 days after the operation, while the chymase activity was increased significantly. After 7 days, the mRNA levels of collagen I, collagen III and fibronectin, all of which are induced by increase of angiotensin II action, were significantly increased in the grafted veins, and the intima-media ratio of the grafted veins was also increased significantly. In the chymase inhibitor-treated group, the chymase activity in the grafted veins 7 days after the operation was strongly suppressed. The elevated mRNA levels of collagen I, collagen III and fibronectin in the grafted veins were suppressed by treatment with the chymase inhibitor, and the intima-media ratio was also decreased significantly. The authors demonstrate that chymase-dependent angiotensin II formation plays an important role in the development of vascular proliferation in the grafted veins.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:309702 HCAPLUS
DOCUMENT NUMBER: 143:452460
TITLE: The suppression effect of chymase inhibitor on aneurysm
AUTHOR(S): Kobayashi, Keiichi; Takai, Shinji; Kin, Tokuo; Muramatsu, Michiko; Katsuma, Takahiro; Miyazaki, Mizuo
CORPORATE SOURCE: Dep. of Surgery, Osaka Medical University, Japan
SOURCE: Ketsuatsu (2005), 12(3), 346-350
CODEN: KETSAH; ISSN: 1340-4598
PUBLISHER: Sentan Igakusha
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The inhibitory effects of the chymase inhibitor Suc-Val-Pro-Phe(p)(OPh) on aneurysm were studied in dogs. The results indicated that chymase mediates angiotensin II and MMP-9 activation in aneurysm.

L27 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:827831 HCAPLUS
DOCUMENT NUMBER: 142:259274
TITLE: The role of chymase in scarring after glaucoma filtration surgery in dogs
AUTHOR(S): Maruichi, Midori
CORPORATE SOURCE: Department of Pharmacology and Department of Ophthalmology, Osaka Medical College, Japan
SOURCE: Osaka Ika Daigaku Zasshi (2004), 63(1), 23-31
CODEN: OIDZAU; ISSN: 0030-6118
PUBLISHER: Osaka Ika Daigaku Igakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Purpose: To determine the role of chymase in scarring after glaucoma filtration surgery in dogs. Methods: A fibroblast cell culture was established from canine Tenon's capsule. The fibroblasts were incubated in the presence of dog chymase (20 ng/mL) or chymase inhibitor Suc-Val-Pro-PheP(OPh)2 (10 μM). Cell proliferation was evaluated by bromodeoxyuridine incorporation. In a canine conjunctival flap model, a sponge treated with Suc-Val-Pro-PheP(OPh)2 or placebo was placed between the conjunctiva

and sclera, and the conjunctival incision was closed. One week after surgery, the degree of adhesion was assessed, chymase activity was measured in the conjunctival and scleral lesions and the areas of the conjunctiva and sclera were measured. Results: Dog chymase significantly increased cell proliferation in the cultured canine Tenon's capsule fibroblasts and this proliferation was completely suppressed by the chymase inhibitor. In the canine surgical model, chymase activity was significantly increased in placebo-treated eyes in corporation to normal eyes, and it was significantly decreased by treatment with the chymase inhibitor. Score for adhesion degree was significantly decreased in the chymase inhibitor-treated eyes in comparison to that in the placebo-treated eyes. The area of conjunctiva in chymase inhibitor-treated eyes was 52.6% as large as that in the placebo-treated eyes. Conclusion: Chymase stimulates proliferation of fibroblasts derived from canine Tenon's capsule, and chymase inhibitor suppresses this stimulation and scarring in the canine conjunctival flap model. These findings suggest that chymase plays an important role in scarring after glaucoma filtration surgery in dogs.

L27 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:783772 HCAPLUS
DOCUMENT NUMBER: 141:406280
TITLE: Effect of Chymase-Dependent Transforming Growth Factor β on Peritoneal Adhesion Formation in a Rat Model
AUTHOR(S): Okamoto, Yukiko; Takai, Shinji; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, 589-8686, Japan
SOURCE: Surgery Today (2004), 34(10), 865-867
CODEN: SUTOE5; ISSN: 0941-1291
PUBLISHER: Springer Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To clarify the role of chymase produced from mast cells, which are closely related to adhesion formation, the authors investigated the preventive effect of a chymase inhibitor on adhesion formation in a rat model. A lesion was created in rats by uterus scraping, and a chymase inhibitor, Suc-Val-Pro-Phep(OPh)2 (10 μM), or a placebo was injected into the abdomen. The level of transforming growth factor β (TGF-β) in the peritoneal fluid was also measured. By 2 wk after the operation, the scores for adhesion formation in the chymase inhibitor-treated group were significantly lower than those in the placebo-treated group, at 1.64 ± 0.34 and 3.27 ± 0.19, resp. ($P < 0.01$). After scraping the uterus, the level of TGF-β in the peritoneal fluid was significantly higher in the placebo-treated group, whereas it was significantly suppressed by the chymase inhibitor. Chymase may play an important role in adhesion formation aided by TGF-β.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:471599 HCAPLUS
DOCUMENT NUMBER: 141:69646
TITLE: Role of chymase on growth of cultured canine Tenon's capsule fibroblasts and scarring in a canine conjunctival flap model
AUTHOR(S): Maruichi, Midori; Takai, Shinji; Sugiyama, Tetsuya; Ueki, Mari; Oku, Hidehiro; Sakaguchi, Masato; Okamoto, Yukiko; Muramatsu, Michiko; Ikeda, Tsunehiko; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College,

Takatsuki City, Osaka, 569-8686, Japan
SOURCE: Experimental Eye Research (2004), 79(1), 111-118
CODEN: EXERA6; ISSN: 0014-4835
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chymase is a chymotrypsin-like serine protease contained in the secretory granules of mast cells. Recently, we reported that chymase activity and the number of chymase-pos. mast cells in conjunctival tissues were significantly increased during the wound healing process in a hamster model of glaucoma surgery. However, it has been unclear the role of chymase on conjunctival scarring. In the present study, we evaluated the effect of dog chymase on cell proliferation of fibroblasts established from canine Tenon's capsule and the effect of a chymase inhibitor on scarring in a canine conjunctival flap model. After a fibroblast cell culture was established from canine Tenon's capsules, the fibroblasts were incubated in the presence of dog chymase (5-20 ng ml-1). Cell proliferation was evaluated by bromodeoxyuridine incorporation. In a canine conjunctival flap model, a sponge treated with a chymase inhibitor, Suc-Val-Pro-PheP(OPh)2, or placebo was placed in between the conjunctiva and sclera and the conjunctival incision was closed. One week after the surgery, adhesion degree was assessed, and chymase activities in the conjunctival lesion and in the areas of the conjunctiva and sclera were measured. In cultured canine Tenon's capsule fibroblasts, dog chymase significantly increased cell proliferation, and this chymase-dependent proliferation was completely suppressed by the chymase inhibitor. In the canine surgical model, chymase activity in placebo-treated eyes was significantly increased compared to control eyes, while it was significantly decreased by treatment with the chymase inhibitor. Scores for adhesion degree in the chymase inhibitor-treated eyes were significantly decreased in comparison with those in placebo-treated eyes. The conjunctival area in the chymase inhibitor-treated eyes was also suppressed to 52·6% compared with that in placebo-treated treated eyes. In conclusion, chymase stimulates proliferation of fibroblasts derived from canine Tenon's capsule and chymase may play an important role in scarring after glaucoma surgery.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

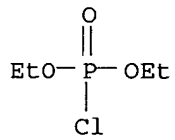
L27 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:213952 HCAPLUS
DOCUMENT NUMBER: 141:16867
TITLE: Topoisomerase I-mediated DNA cleavage as a guide to the development of antitumor agents derived from the marine alkaloid lamellarin D: triester derivatives incorporating amino acid residues
AUTHOR(S): Tardy, Christelle; Facompre, Michael; Laine, William; Baldeyrou, Brigitte; Garcia-Gravalos, Dolores; Francesch, Andres; Mateo, Cristina; Pastor, Alfredo; Jimenez, Jose A.; Manzanares, Ignacio; Cuevas, Carmen; Bailly, Christian
CORPORATE SOURCE: Laboratoire de Pharmacologie Antitumorale du Centre Oscar Lambret, INSERM UR-524, Lille, 59045, Fr.
SOURCE: Bioorganic & Medicinal Chemistry (2004), 12(7), 1697-1712
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:16867

AB The marine alkaloid lamellarin D (LAM-D) has been recently characterized as a potent poison of human topoisomerase I endowed with remarkable cytotoxic activities against tumor cells. The authors report here the first structure-activity relationship study in the LAM-D series. Two groups of triester compds. incorporating various substituents on the three phenolic OH at positions 8, 14 and 20 of 6H-[1]benzopyrano[4',3':4,5]pyrro lo[2,1-a]isoquinolin-6-one pentacyclic planar chromophore typical of the parent alkaloid were tested as topoisomerase I inhibitors. The nonamino compds. in group A showed no activity against topoisomerase I and were essentially noncytotoxic. In sharp contrast, compds. in group B incorporating amino acid residues strongly promoted DNA cleavage by human topoisomerase I. LAM-D derivs. tri-substituted with leucine, valine, proline, phenylalanine or alanine residues, or a related amino side chain, stabilize topoisomerase I-DNA complexes. The DNA cleavage sites detected at T↓G or C↓G dinucleotides with these mols. were identical to that of LAM-D but slightly different from those seen with camptothecin which stimulates topoisomerase I-mediated cleavage at T↓G only. In the DNA relaxation and cleavage assays, the corresponding Boc-protected compds. and the analogs of the nonplanar LAM-501 derivative lacking the 5-6 double bond in the quinoline B-ring showed no effect on topoisomerase I and were considerably less cytotoxic than the corresponding cationic compds. in the LAM-D series. The presence of pos. charges on the mols. enhances DNA interaction but melting temperature studies indicate that DNA binding is not correlated with topoisomerase I inhibition or cytotoxicity. Cell growth inhibition by the 41 lamellarin derivs. was evaluated with a panel of tumor cells lines. With prostate (DU-145 and LN-CaP), ovarian (IGROV and IGROV-ET resistant to ecteinascidin-743) and colon (LoVo and LoVo-Dox cells resistant to doxorubicin) cancer cells (but not with HT29 colon carcinoma cells), the most cytotoxic compds. correspond to the most potent topoisomerase I poisons. The observed correlation between cytotoxicity and topoisomerase I inhibition strongly suggests that topoisomerase I-mediated DNA cleavage assays can be used as a guide to the development of superior analogs in this series. LAM-D is the lead compound of a new promising family of antitumor agents targeting topoisomerase I and the amino acid derivs. appear to be excellent candidates for a preclin. development.

IT 814-49-3, Phosphorochloridic acid, diethyl ester
RL: RCT (Reactant); RACT (Reactant or reagent)
(topoisomerase I-mediated DNA cleavage as guide to development of antitumor agents, marine alkaloid lamellarin D triester derivs. incorporating amino acid residues)

RN 814-49-3 HCAPLUS

CN Phosphorochloridic acid, diethyl ester (8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:262464 HCAPLUS
DOCUMENT NUMBER: 139:127727
TITLE: A novel chymase inhibitor, 4-[1-{[bis-(4-methyl-phenyl)-methyl]-carbamoyl} -3-(2-ethoxy-benzyl)-4-oxo-

azetidine-2- yloxy]-benzoic acid (BCEAB), suppressed cardiac fibrosis in cardiomyopathic hamsters

AUTHOR(S): Takai, Shinji; Jin, Denan; Sakaguchi, Masato; Katayama, Satoru; Muramatsu, Michiko; Sakaguchi, Minoru; Matsumura, Eiko; Kim, Shokei; Miyazaki, Mizuo

CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 305(1), 17-23
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previously, the authors reported that levels of chymase activity and its mRNA in cardiac tissues were significantly increased along with progression of cardiac fibrosis in cardiomyopathic hamsters, but the involvement of chymase in the progression of fibrosis was unclear. In cultured human fibroblasts, the concentration of transforming growth factor-β in the supernatant of medium was significantly increased after injection of human chymase. Furthermore, human chymase dose dependently increased cell proliferation, and this chymase-dependent proliferation was completely suppressed by a chymase inhibitor, Suc-Val-Pro-Phep(OPh)2 (10 μM) or an anti-transforming growth factor-β antibody (100 μg/mL). In this study, the authors used Bio14.6 and F1B hamsters as cardiomyopathic and control hamsters, resp. Cardiomyopathic hamsters were orally administered a novel chymase inhibitor, 4-[1-{[bis-(4-methyl-phenyl)-methyl]-carbamoyl}-3-(2-ethoxy-benzyl)-4-oxo-azetidine-2-yloxy] -benzoic acid (BCEAB; 100 mg/kg per day), or placebo from 5- to 45-wk-old. In the placebo-treated group, the cardiac chymase activity in cardiomyopathic hamsters 45 wk old was significantly increased compared with that in control hamsters. BCEAB significantly reduced the cardiac chymase activity. The indexes (+dP/dt and -dP/dt) of cardiac function were significantly improved by treatment with BCEAB. The mRNA levels of collagen I and collagen III in the placebo-treated hamsters were significantly reduced to 69.6 and 76.5% by treatment with BCEAB, resp. The fibrotic area in cardiac tissues in the BCEAB-treated hamsters was significantly suppressed to 50.7% compared with that in the placebo-treated treated hamsters. Therefore, the activation of transforming growth factor-β by chymase may play an important role in the progression of cardiac fibrosis and cardiac dysfunction in cardiomyopathy.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:260484 HCAPLUS

DOCUMENT NUMBER: 139:286026

TITLE: Suppressant effects of chymase inhibitors on cardiac fibrosis: chymase role in activation of transforming growth factor-β

AUTHOR(S): Takai, Shinji; Kim, Tokuo; Sakaguchi, Masato; Katayama, Tetsu; Muramatsu, Chikao

CORPORATE SOURCE: Dep. of Pharmacology, Osaka Medical University, Japan

SOURCE: Ketsuatsu (2003), 10(3), 251-255
CODEN: KETSAH; ISSN: 1340-4598

PUBLISHER: Sentan Igakusha

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

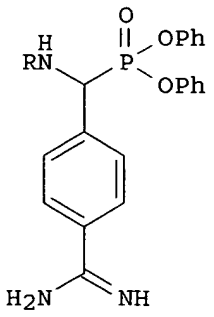
AB The suppressant effects of the chymase inhibitor Suc-Val-

Pro-Phe(OPh)2 on cardiac fibrosis were studied in human fibroblasts in vitro and in hamsters in vivo. The results are discussed with regards to the pathol. role of chymase in activation of transforming growth factor-β in heart fibrosis.

L27 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:749558 HCAPLUS
DOCUMENT NUMBER: 136:15646
TITLE: Significance of chymase-dependent angiotensin II-forming pathway in the development of vascular proliferation
AUTHOR(S): Nishimoto, Masayoshi; Takai, Shinji; Kim, Shokei; Jin, Denan; Yuda, Atsushi; Sakaguchi, Masato; Yamada, Mayumi; Sawada, Yoshihide; Kondo, Keiichiro; Asada, Kunio; Iwao, Hiroshi; Sasaki, Shinjiro; Miyazaki, Mizuo
CORPORATE SOURCE: Dep. Pharmacol., Osaka City Univ. Med. Sch., Osaka, Japan
SOURCE: Circulation (2001), 104(11), 1274-1279
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Vascular tissues of humans and dogs contain chymase as an angiotensin II-forming enzyme. In this study, the authors investigated whether chymase-dependent angiotensin II formation plays a crucial role in the development of vascular proliferation in dog grafted veins. The right external jugular vein of dogs was grafted to the ipsilateral carotid artery. As a control group. the right external jugular veins in dogs that had not received grafts were used. In the chymase inhibitor-treated group, the vein was infiltrated with 10 μM Suc- Val-Pro-PheP(OPh)2 and was grafted to the carotid artery. In the placebo-treated group, ACE activity in the grafted veins was significantly lower than that in the control veins up to 7 days after the operation, whereas chymase activity was increased significantly. After 7 days, the mRNA levels of collagen I, collagen III, and fibronectin, all of which are induced by an increase of angiotensin II action, were significantly increased in the grafted veins, and the intima-media ratio of the grafted veins was also increased. In the chymase inhibitor-treated group, the chymase activity in the grafted veins 7 days after the operation was suppressed to 12.1%. The elevated mRNA levels of fibronectin, collagen I, and collagen III in the grafted veins were significantly suppressed by treatment with the chymase inhibitor, and the intima-media ratio was also decreased significantly. The authors demonstrate for the first time that chymase-dependent angiotensin II formation plays an important role in the development of vascular proliferation in the grafted veins.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:338712 HCAPLUS
DOCUMENT NUMBER: 129:95705
TITLE: Synthesis and Evaluation of Diphenyl Phosphonate Esters as Inhibitors of the Trypsin-like Granzymes A and K and Mast Cell Tryptase
AUTHOR(S): Jackson, Delwin S.; Fraser, Stephanie A.; Ni, Li-Ming; Kam, Chih-Min; Winkler, Ulrike; Johnson, David A.; Froelich, Christopher J.; Hudig, Dorothy; Powers, James C.

CORPORATE SOURCE: School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, 30332-0400, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(13), 2289-2301
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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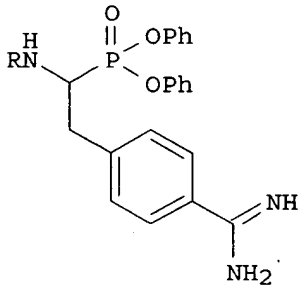


II

AB Thirty-six new amino acid and peptidyl phosphonate esters, e.g. I [R = PhCH2O2C (Cbz), HO2CCH2CH2CO (Suc), R1CH:CHCO, 3-PhOC6H4CO, 2-PhOC6H4CO, 1-C10H7SO2, 1-C10H7CH2O2C, Cbz-X, R2-Pro, Suc-Ala-Ala, Boc-D-Phe-Pro, PhCH2SO2-Gly-Pro; R1 = Ph, 2-furyl, 2-thienyl, 3-pyridyl; X = Ala, Val, Leu, Pro, Thr, Lys, Phe, Ala-Ala, Pro-Ala, Asp-Ala, Asp(OCMe3)-Ala, Lys-Ala, Lys(Boc)-Ala, Phe-Ala, Ala-Ala-Ala; R2 = 2-PhOC6H4CO, 3-PhOC6H4CO, Ph2CHCH2CO, PhCH2CH2CO; Boc = Me3CO2C] were synthesized and evaluated to identify potent and selective inhibitors for four trypsin-like proteases: lymphocyte granzymes A and K, human mast cell tryptase, and pancreatic trypsin. Among five Lys and Arg homologs, II (R = Cbz) is the most potent inhibitor for granzyme A, and CbzNHCH(PO3Ph2)(CH2)4NH2.HCl (III) is the best inhibitor for granzyme K, mast tryptase, and trypsin. Generally, phosphonates I inhibit granzyme A and trypsin more potently than granzyme K and tryptase. Dipeptide phosphonates I (R = Cbz-Ala, Cbz-Thr) are the most potent inhibitors for granzyme A, and I (R = Cbz-Thr) (kobs/[I] = 2220 M-1 s-1) was quite specific with much lower inhibition rates for granzyme K and trypsin (kobs/[I] = 3 and 97 M-1 s-1, resp.) and no inhibition with tryptase. The most effective inhibitor of granzyme A was I (R = PhCH2SO2-Gly-Pro) with a second-order rate constant of 3650 M-1 s-1. The most potent inhibitor for granzyme K was I (R = Ph2CHCH2CO-Pro) with a kobs/[I] = 1830 M-1 s-1; all other phosphonates inhibited granzyme K weakly (kobs/[I] < 60 M-1 s-1). Human mast cell tryptase was inhibited slowly by these phosphonates with III as the best inhibitor (kobs/[I] = 89 M-1 s-1). The overall results suggest that scaffolds of II (R = Phe-Thr) and Phe-Pro-Lys will be useful to create selective phosphonate inhibitors for granzymes A and K, resp., and that P4 substituents offer opportunities to further enhance selectivity and reactivity.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:218259 HCAPLUS
DOCUMENT NUMBER: 112:218259
TITLE: Phosphorus state in ion exchangers according to phosphorus-31 NMR data
AUTHOR(S): Randarevich, S. B.; Zhukova, N. G.; Korovin, V. Yu.; Polyakova, O. P.; Laskorin, B. N.
CORPORATE SOURCE: Inst. Obshch. Neorg. Khim., Dneprodzerzhinsk, USSR
SOURCE: Doklady Akademii Nauk SSSR (1989), 307(4), 906-12 [Phys. Chem.]
CODEN: DANKAS; ISSN: 0002-3264
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB The state of P in various ion exchangers (SF-5, KMDF-3, VPF, AFI-21, AFI-22, AFI-24, AFI-5, AFI-7, NFOS, (glycidyl methacrylate-based resins) was studied by 31P NMR using 85% H3PO4 as a reference The selectivity and sorption capacity of the ion exchangers in the recovery and concentration of nonferrous, rare, and radioactive metals are largely dependent on the state of P in the polymer matrix.

IT 9043-76-9 127238-89-5
RL: USES (Uses)
(ion exchangers, for recovery of nonferrous and rare and radioactive metals by, phosphorus state in relation to)

RN 9043-76-9 HCAPLUS
CN Phosphonic acid, ethenyl-, bis(2-chloroethyl) ester, polymer with diethenylbenzene (9CI) (CA INDEX NAME)

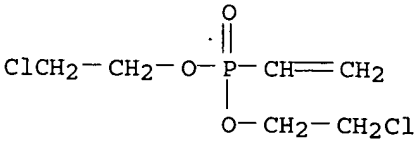
CM 1

CRN 1321-74-0
CMF C10 H10
CCI IDS

2 [D1—CH═CH2]

CM 2

CRN 115-98-0
CMF C6 H11 Cl2 O3 P



RN 127238-89-5 HCAPLUS

CN Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester, polymer with 5-ethenyl-2-methylpyridine (9CI) (CA INDEX NAME)

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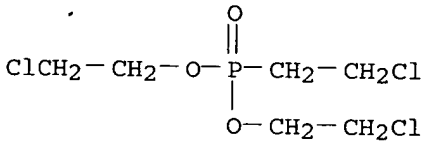
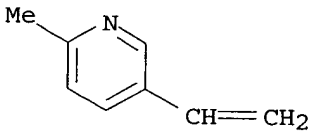
CRN 6294-34-4
CMF C6 H12 Cl3 O3 P



CM 2

CRN 140-76-1
CMF C8 H9 N



L27 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:492705 HCAPLUS
DOCUMENT NUMBER: 111:92705
TITLE: Irreversible inhibition of serine proteases by peptidyl derivatives of α-aminoalkylphosphonate diphenyl esters
AUTHOR(S): Oleksyszyn, Jozef; Powers, James C.
CORPORATE SOURCE: Sch. Chem., Georgia Inst. Technol., Atlanta, GA, 30332, USA
SOURCE: Biochemical and Biophysical Research Communications (1989), 161(1), 143-9
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peptidyl α- aminoalkylphosphonate di-Ph esters were synthesized and shown to be effective inhibitors of serine proteases. Extending the peptide chain from a single α-aminoalkylphosphonate residue to a tripeptide or tetrapeptide derivative resulted in a 65-2800-fold improvement in inhibitory potency and in increased specificity. The rate of inactivation of chymotrypsin by MeO-Suc-Ala-Ala-Pro-HNCH(CH2Ph)P(O)(OPh)2 was decreased 5-fold in the presence of the substrate, Suc-Val-Pro-Phe-NA (0.119 mM) (Suc = succinyl; NA = 4-nitroanilide). Phosphonylated serine proteases were extremely stable since the half-life for reactivation was >48 h for inhibited elastases and ≥10 h for chymotrypsin.

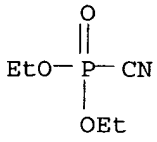
L27 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1976:31472 HCAPLUS

DOCUMENT NUMBER: 84:31472
TITLE: Diphenyl phosphorazidate (DPPA) and diethyl phosphorocyanidate (DEPC). Two new reagents for solid-phase peptide synthesis and their application to the synthesis of porcine motilin
AUTHOR(S): Yamada, Shunichi; Ikota, Nobuo; Shioiri, Takayuki; Tachibana, Shinro
CORPORATE SOURCE: Fac. Pharm. Sci., Univ. Tokyo, Tokyo, Japan
SOURCE: Journal of the American Chemical Society (1975), 97(24), 7174-5
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The coupling reactivity of N3P(O)(OPh)2 (I) and NCP(O)(OEt)2 (II) were higher than that of dicyclohexylcarbodiimide in DMF but lower in CH2Cl2. Me3CO2C-Pro-Leu-Gly-NH2, prepared by stepwise solid phase synthesis, was obtained in 70 and 76% yields using I and II, resp., in DMF containing Et3N. Motilin, with natural biol. activity, was prepared by the solid phase fragment condensation of Gln-Glu(OCH2Ph)-Lys(CO2CH2C6H4Cl-2)-Glu(OCH2Ph)-Arg(NO2)-Asn-Lys(CO2CH2C6H4Cl-2)-Gly-Gln-resin, Me3CO2C-Leu-Gln-Arg(NO2)-Met, Me3CO2C-Glu(OCH2Ph)-OH, and PhCH2O2C-Phe-Val-Pro-Ile-Phe-Thr(CH2Ph)-Tyr(CH2Ph)-Gly with II in DMF containing Et3N.

IT 2942-58-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(peptide coupling reagent, reactivity of)

RN 2942-58-7 HCAPLUS
CN Phosphorocyanidic acid, diethyl ester (8CI, 9CI) (CA INDEX NAME)



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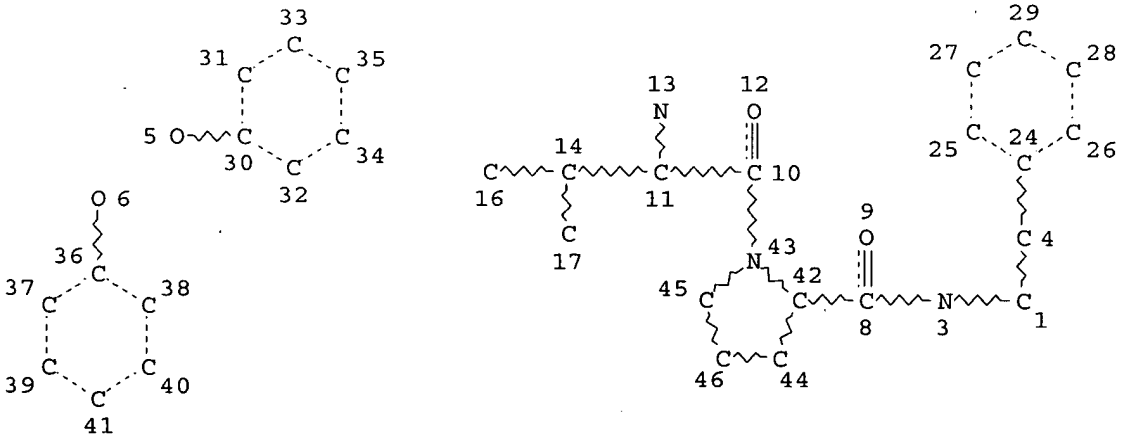

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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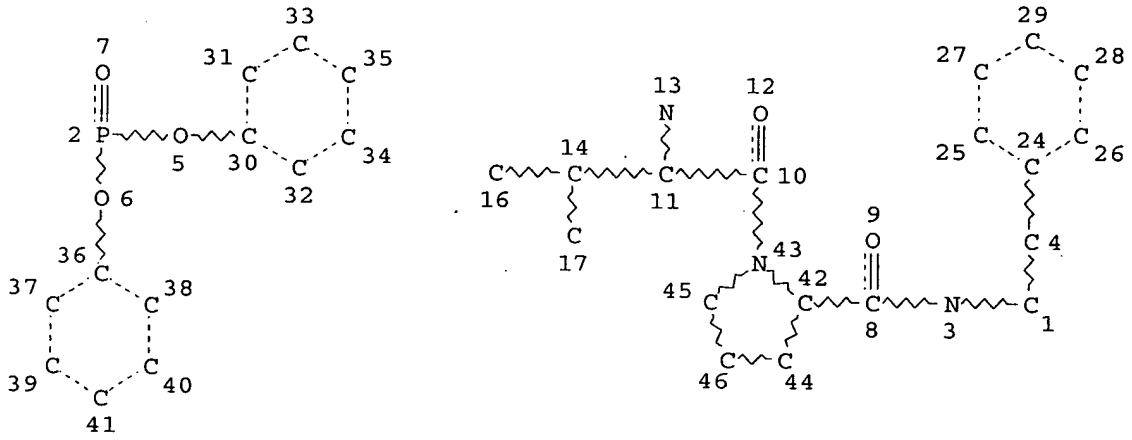
L7 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 39

STEREO ATTRIBUTES: NONE
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L9 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L8
L10 176900 SEA FILE=REGISTRY ABB=ON PLU=ON VPF/SQSP
L11 21544 SEA FILE=REGISTRY ABB=ON PLU=ON PHOSPHONATE/BI
L12 267 SEA FILE=REGISTRY ABB=ON PLU=ON L6 NOT L8
L13 214 SEA FILE=HCAPLUS ABB=ON PLU=ON L12
L14 91667 SEA FILE=HCAPLUS ABB=ON PLU=ON L11 OR ?PHOSPHONAT?
L15 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L13 AND L14
L16 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 NOT L9
L17 22549 SEA FILE=HCAPLUS ABB=ON PLU=ON L10
L24 1075 SEA FILE=HCAPLUS ABB=ON PLU=ON VPF OR VAL?(2W)PRO?(2W)PHE?
L25 99302 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 OR OPH
L26 26 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND L25
L27 14 SEA FILE=HCAPLUS ABB=ON PLU=ON L26 NOT (L9 OR L16)
L34 453 SEA FILE=HCAPLUS ABB=ON PLU=ON MIYAZAKI M/AU OR MIYAZAKI MIZUO/AU
L35 1 SEA FILE=HCAPLUS ABB=ON PLU=ON (L34 AND (L13 OR L14 OR L17 OR L24 OR L25)) NOT (L9 OR L16 OR L27)

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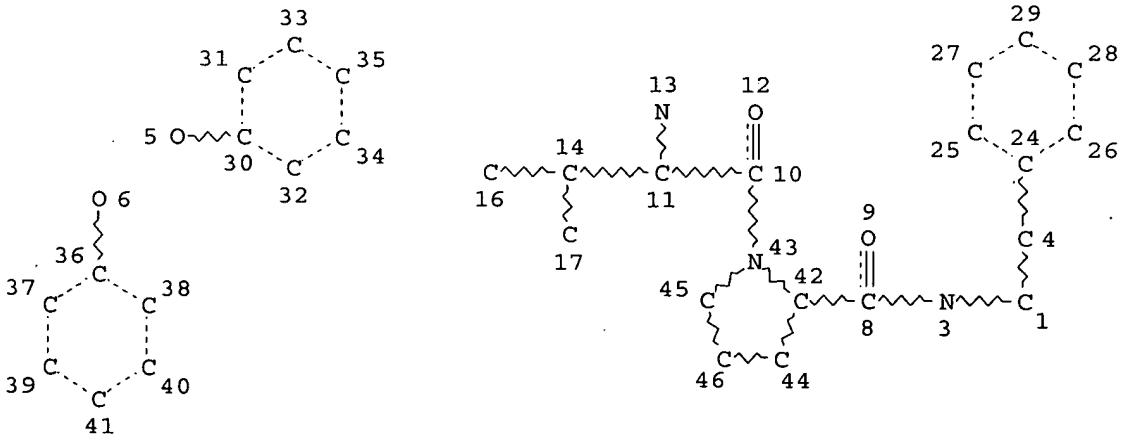
L35 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:162874 HCAPLUS
DOCUMENT NUMBER: 134:360985
TITLE: Non-Peptidic inhibitors of human chymase. Synthesis, structure-activity relationships, and pharmacokinetic profiles of a series of 5-amino-6-oxo-1,6-dihydropyrimidine-containing trifluoromethyl ketones
AUTHOR(S): Akahoshi, F.; Ashimori, A.; Yoshimura, T.; Imada, T.; Nakajima, M.; Mitsutomi, N.; Kuwahara, S.; Ohtsuka, T.; Fukaya, C.; Miyazaki, M.; Nakamura, N.
CORPORATE SOURCE: Drug Discovery Laboratories, Welfide Corporation, Hirakata, Osaka, 573-1153, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(2), 301-315
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:360985

AB Chymase possesses a wide variety of actions, including promotion of angiotensin II production and histamine release from mast cells. However, due to a lack of effective inhibitors featuring both high inhibitory activity and high metabolic stability, the pathophysiol. role of chymase has not been fully elucidated. We designed non-peptidic inhibitors based on the predicted binding mode of the peptidic chymase inhibitor Val-Pro-Phe-CF3 and demonstrated that the Val-Pro unit is replaceable with a (5-amino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl)acetyl moiety. Structure-activity relation studies revealed that Ph substitution at the 2-position of the pyrimidinone ring is indispensable for high activity. The most potent compound with Ki=0.0506 μM is superior in potency to the parent peptidic inhibitor Val-Pro-Phe-CF3 and has good selectivity for chymase over other proteases. One related analog was orally absorbed and maintained high plasma levels for at least 2 h. These results suggest that the derivs. reported here could be developed as agents for treatment of chymase-induced disease.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> => d stat que l36
L4 STR

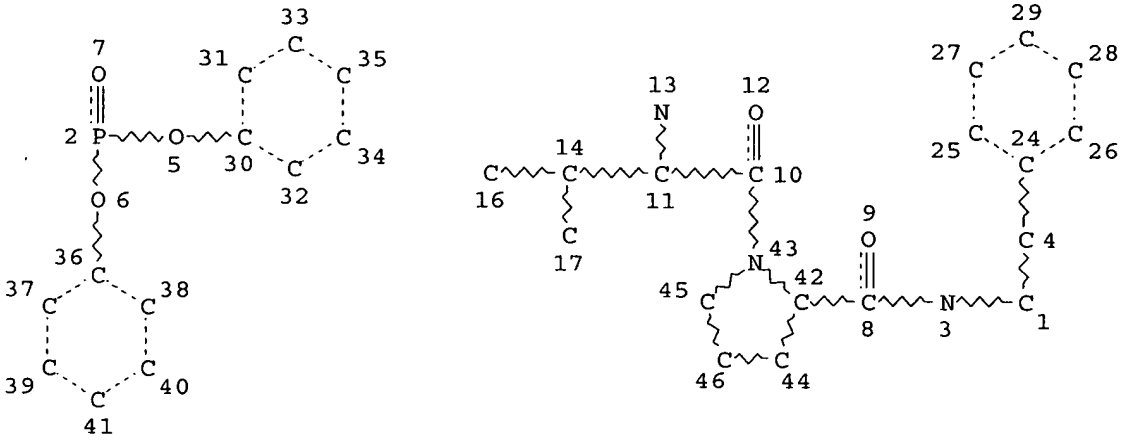


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 37

STEREO ATTRIBUTES: NONE
L6 273 SEA FILE=REGISTRY SSS FUL L4
L7 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 39

STEREO ATTRIBUTES: NONE

L8	6	SEA FILE=REGISTRY SUB=L6 SSS FUL L7
L9	16	SEA FILE=HCAPLUS ABB=ON PLU=ON L8
L10	176900	SEA FILE=REGISTRY ABB=ON PLU=ON VPF/SQSP
L11	21544	SEA FILE=REGISTRY ABB=ON PLU=ON PHOSPHONATE/BI
L12	267	SEA FILE=REGISTRY ABB=ON PLU=ON L6 NOT L8
L13	214	SEA FILE=HCAPLUS ABB=ON PLU=ON L12
L14	91667	SEA FILE=HCAPLUS ABB=ON PLU=ON L11 OR ?PHOSPHONAT?
L15	1	SEA FILE=HCAPLUS ABB=ON PLU=ON L13 AND L14
L16	1	SEA FILE=HCAPLUS ABB=ON PLU=ON L15 NOT L9
L17	22549	SEA FILE=HCAPLUS ABB=ON PLU=ON L10
L22	18010	SEA FILE=HCAPLUS ABB=ON PLU=ON ?ADHES?(L)TISSUE
L24	1075	SEA FILE=HCAPLUS ABB=ON PLU=ON VPF OR VAL?(2W)PRO?(2W)PHE?
L25	99302	SEA FILE=HCAPLUS ABB=ON PLU=ON L14 OR OPH
L26	26	SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND L25
L27	14	SEA FILE=HCAPLUS ABB=ON PLU=ON L26 NOT (L9 OR L16)
L34	453	SEA FILE=HCAPLUS ABB=ON PLU=ON MIYAZAKI M/AU OR MIYAZAKI MIZUO/AU
L35	1	SEA FILE=HCAPLUS ABB=ON PLU=ON (L34 AND (L13 OR L14 OR L17 OR L24 OR L25)) NOT (L9 OR L16 OR L27)
L36	4	SEA FILE=HCAPLUS ABB=ON PLU=ON (L34 AND L22) NOT (L9 OR L16 OR L27 OR L35)

=> d ibib abs hitstr l36 1-4

L36 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:814642 HCAPLUS
DOCUMENT NUMBER: 141:325061
TITLE: Therapeutic applications of chymase inhibitors in cardiovascular diseases and fibrosis
AUTHOR(S): Takai, Shinji; Jin, Denan; Muramatsu, Michiko; Okamoto, Yukiko; Miyazaki, Mizuo
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Takatsuki City, Osaka, 569-8686, Japan
SOURCE: European Journal of Pharmacology (2004), 501(1-3), 1-8
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Chymase activates not only angiotensin I to angiotensin II but also latent transforming growth factor-β-binding protein to transforming growth factor-β. In dog grafted veins, chymase activity and angiotensin II concentration along with vascular proliferation were significantly increased, while they were significantly suppressed by a chymase inhibitor. After balloon injury in dog arteries, chymase activity was significantly increased in the injured artery, and a chymase inhibitor and an angiotensin AT1 receptor antagonist were effective in preventing the vascular proliferation, but an angiotensin-converting enzyme inhibitor was ineffective. In fibrotic models, the tissue fibrosis was reduced by chymase inhibitors. In adhesion models, the transforming growth factor-β concentration and adhesion formation were suppressed by chymase inhibitors. Therefore, chymase inhibitors may be useful for preventing cardiovascular diseases and fibrosis via inhibition of angiotensin II formation and transforming growth factor-β activation.
REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:532523 HCAPLUS
DOCUMENT NUMBER: 139:74093
TITLE: Remedies or preventives for diseases in association with tissue fibrosis
INVENTOR(S): Miyazaki, Mizuo; Kamoshita, Keiichi; Sukenaga, Yoshikazu; Suzuki, Yoshikazu; Mashiba, Hiroko; Matsumoto, Tetsuya
PATENT ASSIGNEE(S): Nippon Kayaku Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055488	A1	20030710	WO 2002-JP13681	20021226

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT,

LU, MC, NL, PT, SE, SI, SK, TR

JP 2003192594	A2	20030709	JP 2001-396902		20011227
JP 2003238408	A2	20030827	JP 2002-32670		20020208
AU 2002367143	A1	20030715	AU 2002-367143		20021226
PRIORITY APPLN. INFO.:			JP 2001-396902	A	20011227
			JP 2002-32670	A	20020208
			WO 2002-JP13681	W	20021226

OTHER SOURCE(S): MARPAT 139:74093

AB Disclosed are remedies or preventives for diseases in association with fibrosis in tissues such as tissue fibrosis or disorders during wound healing such as adhesion or scar, which contain as the active ingredient a compound having a pyrimidone skeleton and showing a chymase inhibitory activity or pharmacol. acceptable salts thereof, for example, 2-(5-formylamino-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl)-N-[2,3-dioxo-1-phenylmethyl-6-(2-pyridyloxy)]hexylacetamide or its pharmaceutically acceptable salt. Oral administration of these drugs can effectively contribute to the treatment or prevention the above diseases.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:411492 HCAPLUS
DOCUMENT NUMBER: 138:19331
TITLE: Antiatherosclerotic efficacy of olmesartan
AUTHOR(S): Miyazaki, M.; Takai, S.
CORPORATE SOURCE: Department of Pharmacology, Osaka Medical College, Osaka, 569-8686, Japan
SOURCE: Journal of Human Hypertension (2002), 16(Suppl. 2), S7-S12
CODEN: JHHYEN; ISSN:, 0950-9240
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The possible inhibition of lipid deposition into vascular tissues by a novel angiotensin II type 1 receptor antagonist, olmesartan, was investigated in a primate high-cholesterol model. Twelve monkeys that were fed a high-cholesterol (4% cholesterol and 6% corn oil) diet for 6 mo were divided into two groups: one group was given olmesartan medoxomil (10 mg/kg per day), and the other group was given no medication. A further control group of six monkeys was fed a normal diet throughout the study. The level of low-d. lipoprotein (LDL) cholesterol was increased by the high-cholesterol diet, whereas that of high-d. lipoprotein (HDL) cholesterol was decreased. Olmesartan decreased the areas of lipid deposition on the aortic surface and intimal cross-section area, but not the mean blood pressure and the levels of LDL and HDL cholesterol. The relaxation response of isolated carotid arteries to acetylcholine was suppressed in the high-cholesterol group, but this was improved by olmesartan. Olmesartan inhibited the accumulation of macrophages in the intimal layer. Serum levels of transforming growth factor (TGF)-β1, macrophage colony-stimulating factor (M-CSF) and intracellular adhesion mol. (ICAM)-1 were increased in monkeys fed the high-cholesterol diet, but they were suppressed by olmesartan, although the decrease was not significant. Olmesartan reduced lipid deposition, accompanied by the improvement of vascular functions and the inhibition of macrophage accumulation in the intimal layer and showed a trend towards the suppression of serum TGF-β1, M-CSF and ICAM-1.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:413273 HCAPLUS
DOCUMENT NUMBER: 133:279800
TITLE: Association between the Expression of Mast Cell Chymase and Intraperitoneal Adhesion Formation in Mice
AUTHOR(S): Yao, Yu-Lin; Ishihara, Takafumi; Takai, Shinji; Miyazaki, Mizuo; Mita, Shiro
CORPORATE SOURCE: Discovery Research Division, Nara Research and Development Center, Santen Pharmaceutical Co., Ltd., Ikoma-shi, Nara, 630-0101, Japan
SOURCE: Journal of Surgical Research (2000), 92(1), 40-44
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Adhesion formation is a major source of postoperative morbidity and mortality. Mast cells and their major protease, chymase, have been shown to participate in the healing process as well as in tissue remodeling. We aimed to identify the role of mast cells in i.p. adhesion formation and to assess whether there is an association between the expression of mast cell chymase and adhesion formation. Materials and methods: Both mast cell-deficient W/WV mice and congenic +/+ mice received a standardized lesion produced by cecal scraping and the application of 95% ethanol. Adhesions were assessed blindly 1 wk later using a standardized scale. In addition, histamine content, mast cell nos., and chymase activity in cecum as well as at the healing sites were evaluated before and 7 days after surgical injury. Results: A significant reduction in adhesion formation was seen in mast cell-deficient W/WV mice ($P < 0.05$). In the normal cecum, histamine content did not significantly differ between W/WV and +/+ mice. Chymase activity in cecum was detected in control +/+ mice, but not in W/WV mice. Mast cell nos. and chymase activity levels at the healing sites of +/+ mice were significantly increased 7 days after surgery. Conclusions: Our results indicate that mast cells contribute to i.p. adhesion formation in mice, and suggest that chymase originating from mast cells is important in the development of adhesions. (c) 2000 Academic Press.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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